

UTILITY PATENT APPLICATION TRANSMITTAL (Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
CG/13180.18

Total Pages in this Submission
3

TO THE ASSISTANT COMMISSIONER FOR PATENTS

**Box Patent Application
Washington, D.C. 20231**

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY.

and invented by:

**Guy A. Rouleau;
Ronald G. Lafrenière; and
Daniel Rochefort**

If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: _____

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Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 140 pages and including the following:
 - a. ☒ Descriptive Title of the Invention
 - b. ☐ Cross References to Related Applications (if applicable)
 - c. ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
 - d. ☐ Reference to Microfiche Appendix (if applicable)
 - e. ☒ Background of the Invention
 - f. ☒ Brief Summary of the Invention
 - g. ☒ Brief Description of the Drawings (if drawings filed)
 - h. ☒ Detailed Description
 - i. ☒ Claim(s) as Classified Below
 - j. ☒ Abstract of the Disclosure
 - k. Annex for list of sequences

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

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Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
a. ☐ Formal b. ☒ Informal Number of Sheets 21
4. ☒ Oath or Declaration
a. ☐ Newly executed *(original or copy)* ☒ Unexecuted
b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
c. ☒ With Power of Attorney ☐ Without Power of Attorney
d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under
Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby
incorporated by reference therein.
6. ☐ Computer Program in Microfiche
7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*
a. ☐ Paper Copy
b. ☐ Computer Readable Copy
c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☐ Certificate of Mailing
☐ First Class ☐ Express Mail *(Specify Label No.):* _____

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Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. ☐ Small Entity Statement(s) - Specify Number of Statements Submitted: _____
17. ☐ Additional Enclosures (please identify below):

LIST OF SEQUENCES (1-98)

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	13	- 20 =	0	x \$11.00	\$0.00
Indep. Claims	6	- 3 =	3	x \$40.00	\$120.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$355.00
OTHER FEE (specify purpose) _____					\$0.00
TOTAL FILING FEE					\$475.00

- ☐ A check in the amount of _____ to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 07-1742 as described below. A duplicate copy of this sheet is enclosed.
- ☒ Charge the amount of \$475.00 as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: _____

Marc Lupien
Reg No. 40461

Signature

cc:

TITLE OF THE INVENTION

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY,
MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS,
DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY

5 FIELD OF THE INVENTION

The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three loci mapping to chromosome 2, which show a linkage with epilepsy in patients. The
10 invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA), to variations and mutations in these sequences and to the use thereof to assess, diagnose, prognosis or treat epilepsy.

BACKGROUND OF THE INVENTION

Epilepsy is one of the most common neurological
15 conditions, occurring in about 1.0% of the general population. The disease is characterised by paroxysmal abnormal electrical discharges in the brain, which lead to transient cerebral dysfunction in the form of a seizure. A seizure is considered partial when the epileptic discharge is limited to part of one brain hemisphere, or generalised when it involves
20 both cerebral hemispheres at the onset. The current classification of the epileptic syndromes rests on two criteria: 1) seizure type which may be generalised or partial at the onset, according to clinical and EEG features; and 2) etiology, which may be idiopathic, cryptogenic and symptomatic. Symptomatic epilepsies have multiple and heterogeneous causes including
25 brain injury, CNS infection, migrational and metabolic disorders. In the majority (65%) of the patients with either generalised or partial epilepsy, there is no underlying cause (idiopathic) or the cause is thought to be hidden or

occult (cryptogenic). Also, in the idiopathic epileptic syndromes, there is no evidence of cerebral dysfunction other than the seizure, and the neurological examination is normal. There is now increasing evidence that in this latter group, genetic factors are important, especially for the idiopathic generalised epilepsy (IGE). In a recent study, Berkovic et al (1998) showed a 62% concordance rate in monozygotic twins overall for epilepsy. In this study, a higher concordance rate has been found in the generalised compared to the partial epilepsies, with 76% concordance rate for IGE. Recent studies using molecular genetic approaches have shown that many susceptibility genes for the epilepsies in human involve membrane ion channel and related proteins. These studies include the syndrome of benign familial neonatal convulsions where two loci have been identified [EBN1 on chromosome 20, the KCNQ2 gene (a potassium channel); and EBN2 on chromosome 8, the KCNQ3 gene (also a potassium channel)] (Bievert et al, 1998; Charlier et al, 1998; Singh et al, 1998), as well as autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE - chromosome 20, and the CHRNA4 gene (the neuronal nicotinic acetylcholine receptor alpha 4 subunit)] (Steinlein et al, 1995). More recently, there was a clinical description of a new syndrome (GEFS), which consisted of generalised epilepsy with febrile seizures. According to the current classification of epileptic syndrome, this syndrome would fall in the category of IGE, based on the seizure and electroencephalographic features. However, febrile seizures were present in all probands with GEFS, and the pattern of inheritance was clearly autosomal dominant, which are not part of the usual IGE phenotype. This unique GEFS syndrome has been shown to be associated with a mutation on the beta-1 subunit of brain voltage-gated sodium channel (SCN1B) gene (Wallace et al, 1998). In addition, three different groups, including the group of the present inventors, have identified another locus on chromosome 2 in large kindred with this specific syndrome (GEFS). This region contains many

candidate genes, including a cluster of alpha subunits of sodium channels (SCNA). Voltage-gated sodium channels play an important role in the generation of action potential in nerve cells and muscle. The alpha subunit (SCNA) is the main component of the channel, and would be sufficient to
 5 generate an efficient channel when expressed in cells *in vitro*. In turn, the beta-1 and 2 subunits need an alpha subunit to give an effective channel. The role of these subunits would be to modify the kinetic properties of the channel, mainly by fast inactivation of the sodium currents. The mutation found in the GEFS syndrome on the SCN1B gene was shown to reduce
 10 the fast inactivation of the sodium channels as compared to a normal SCNB1, when co-expressed with an alpha subunit. It is probable that this could be the mechanism by which the mutation induce an hyperexcitability state in the brain, leading to seizure in humans. Interestingly, the mechanism of action of most of the anticonvulsant drugs is through a reduction of the repetitive firing of neurons, which is also known to be
 15 dependent on fast inactivation. These finding make it likely that additional epilepsy genes will be identified by mutations in ion channels.

There thus remains a need to identify whether IGE is caused by a mutation in a sodium channel (SCNA). There also remains a
 20 need to assess whether a mutation(s) in SCNA is associated with GEFs. There also remains a need to determine whether a mutation that affects the fast inactivation of a sodium channel, given the particular phenotype of GEFS or IGE, could be linked to a region which includes SCNA genes.

The present invention seeks to meet these and other
 25 needs.

The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

In one embodiment, the present invention relates to a genetic assay for determining predisposition to epilepsy.

5 In another embodiment, the present invention relates to a use of at least one of the loci of the present invention or an equivalent thereof (e.g. a loci in linkage disequilibrium therewith) as a marker for epilepsy and to determine the optimal treatment thereof (e.g. to guide the treatment modalities, thereby optimizing treatment to a particular clinical situation).

10 Yet in another embodiment, the present invention relates to an assay to screen for drugs for the treatment and/or prevention of epilepsy. In a particular embodiment, such assays can be designed using cells from patients having a known genotype at one of the loci of the present invention. These cells harboring recombinant vectors can enable
15 an assessment of the functionality of the SCN1A, and/or SCN2A and/or SCN3A and a combination thereof. Non-limiting examples of assays that could be used in accordance with the present invention include *cis-trans* assays similar to those described in U.S.P. 4,981,784.

It shall be understood that the determination of allelic
20 variations in at least one of the loci of the present invention can be combined to the determination of allelic variation in other gene/markers linked to a predisposition to epilepsy. This combination of genotype analyses could lead to better diagnosis programs and/or treatment of epilepsy. Non-limiting examples of such markers include SCN1B, EBN1,
25 KCNQ2, EBN2, KCNQ3, ADFLE and CHRNA4.

In accordance with the present invention, there is therefore provided a method of determining an individual's predisposition to epilepsy, which comprises determining the genotype of at least one locus selected from the group consisting of SCN1A, SCN2A and SCN3A.

In one particular embodiment, the present invention provides a method of determining an individual's predisposition to epilepsy, which comprises determining a polymorphism (directly or indirectly by linkage disequilibrium) in a biological sample of an individual and analyzing the allelic variation in at least one of the loci selected from SCN1A, SCN2A and SCN3A, thereby determining an individual's predisposition to epilepsy.

In accordance with the present invention, there is also provided a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

Also provided within the present invention is a compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene, wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

SCN1A, SCN2A and SCN3A refers to genes and proteins for Sodium Channel, Neuronal Type I, Alpha Subunit isoforms, and are described at OMIM # 182389 (Online Mendelian Inheritance in Man). These genes are structurally distinct sodium channel alpha-subunit

isoforms in brain, also known as brain types I, II and III, respectively. Gene, cDNA and protein sequences for the various isoforms are shown in SEQ ID NOS:1-98.

Numerous methods for determining a genotype are known and available to the skilled artisan. All these genotype determination methods are within the scope of the present invention. In a particular embodiment of a method of the present invention, the determination of the genotype comprises an amplification of a segment of one of the loci selected from the group consisting of SCN1A, SCN2A and SCN3A and in a particularly preferred embodiment, the amplification is carried out using polymerase chain reaction.

In a particular embodiment, a pair of primers is designed to specifically amplify a segment of one of the markers of the present invention. This pair of primers is preferably derived from a nucleic acid sequence of SCN1A, SCN2A or SCN3A or from sequences flanking these genes, to amplify a segment of SCN1A, SCN2A or SCN3A (or to amplify a segment of a loci in linkage disequilibrium with at least one of the loci of the present invention). While a number of primers are exemplified herein, other primer pairs can be designed, using the sequences of the SCN1A, SCN2A and SCN3A nucleic acids molecules described hereinbelow. The same would apply to primer pairs from loci in linkage disequilibrium with the markers of the present invention.

Restriction fragment length polymorphisms can be used to determine polymorphisms at the SCN1A, SCN2A and SCN3A loci (and equivalent loci).

While human SCN1A, SCN2A and SCN3A are preferred sequences (nucleic acid and proteins) in accordance with the present invention, the invention should not be so limited. Indeed, in view of the significant conservation of these genes throughout evolution,

sequences from different species, and preferably mammalian species, could be used in the assays of the present invention. One non-limiting example is the rat SCN1A ortholog gene which shows 95% identity with the human SCN1A gene. The significant conservation of the mouse

5 SCN1A gene can also be observed in OMIM (see above).

In order to provide a clear and consistent understanding of terms used in the present description, a number of definitions are provided hereinbelow.

10 As used herein the term "RFLP" refers to restriction fragment length polymorphism.

The terms "polymorphism", "DNA polymorphism" and the like, refer to any sequence in the human genome which exists in more than one version or variant in the population.

15 The term "linkage disequilibrium" refers to any degree of non-random genetic association between one or more allele(s) of two different polymorphic DNA sequences, that is due to the physical proximity of the two loci. Linkage disequilibrium is present when two DNA segments that are very close to each other on a given chromosome will tend to remain unseparated for several generations with the consequence

20 that alleles of a DNA polymorphism (or marker) in one segment will show a non-random association with the alleles of a different DNA polymorphism (or marker) located in the other DNA segment nearby. Hence, testing of a marker in linkage disequilibrium with the polymorphisms of the present invention at the SCN1A, SCN2A and/or

25 SCN3A genes (indirect testing), will give almost the same information as testing for the SCN1A, SCN2A and SCN3A polymorphisms directly. This situation is encountered throughout the human genome when two DNA polymorphisms that are very close to each other are studied. Linkage disequilibriums are well known in the art and various degrees of linkage

disequilibrium can be encountered between two genetic markers so that some are more closely associated than others.

It shall be recognized by the person skilled in the art to which the present invention pertains, that since some of the
 5 polymorphisms or mutations herein identified in the SCN1A, SCN2A and/or SCN3A genes can be within the coding region of the genes and therefore expressed, that the present invention should not be limited to the identification of the polymorphisms/mutations at the DNA level (whether on genomic DNA, amplified DNA, cDNA, or the like). Indeed,
 10 the herein-identified polymorphisms and/or mutations could be detected at the mRNA or protein level. Such detections of polymorphism identification on mRNA or protein are known in the art. Non-limiting examples include detection based on oligos designed to hybridize to mRNA or ligands such as antibodies which are specific to the encoded polymorphism (i.e.
 15 specific to the protein fragment encoded by the distinct polymorphisms).

Nucleotide sequences are presented herein by single strand, in the 5' to 3' direction, from left to right, using the one letter nucleotide symbols as commonly used in the art and in accordance with the recommendations of the IUPAC-IUB Biochemical Nomenclature
 20 Commission.

Unless defined otherwise, the scientific and technological terms and nomenclature used herein have the same meaning as commonly understood by a person of ordinary skill to which this invention pertains. Generally, the procedures for cell cultures,
 25 infection, molecular biology methods and the like are common methods used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook et al. (1989, Molecular Cloning - A Laboratory Manual, Cold Spring Harbor Laboratories) and Ausubel et al. (1994, Current Protocols in Molecular Biology, Wiley, New York).

The present description refers to a number of routinely used recombinant DNA (rDNA) technology terms. Nevertheless, definitions of selected examples of such rDNA terms are provided for clarity and consistency.

- 5 As used herein, “nucleic acid molecule”, refers to a polymer of nucleotides. Non-limiting examples thereof include DNA (i.e. genomic DNA, cDNA, RNA molecules (i.e. mRNA) and chimeras of DNA and RNA. The nucleic acid molecule can be obtained by cloning techniques or synthesized. DNA can be double-stranded or
10 single-stranded (coding strand or non-coding strand [antisense]).

The term “recombinant DNA” as known in the art refers to a DNA molecule resulting from the joining of DNA segments. This is often referred to as genetic engineering.

- The term “DNA segment”, is used herein, to refer to a
15 DNA molecule comprising a linear stretch or sequence of nucleotides. This sequence when read in accordance with the genetic code, can encode a linear stretch or sequence of amino acids which can be referred to as a polypeptide, protein, protein fragment and the like.

- The terminology “amplification pair” refers herein to a
20 pair of oligonucleotides (oligos) of the present invention, which are selected to be used together in amplifying a selected nucleic acid sequence by one of a number of types of amplification processes, preferably a polymerase chain reaction. Other types of amplification processes include ligase chain reaction, strand displacement
25 amplification, or nucleic acid sequence-based amplification, as explained in greater detail below. As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions.

The nucleic acid (i.e. DNA, RNA or chimeras thereof) for practicing the present invention may be obtained according to well known methods.

Oligonucleotide probes or primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted genomes employed. In general, the oligonucleotide probes or primers are at least 12 nucleotides in length, preferably between 15 and 24 molecules, and they may be adapted to be especially suited to a chosen nucleic acid amplification system. As commonly known in the art, the oligonucleotide probes and primers can be designed by taking into consideration the melting point of hybridization thereof with its targeted sequence (see below and in Sambrook et al., 1989, Molecular Cloning -A Laboratory Manual, 2nd Edition, CSH Laboratories; Ausubel et al., 1989, in Current Protocols in Molecular Biology, John Wiley & Sons Inc., N.Y.).

The term "DNA" molecule or sequence (as well as sometimes the term "oligonucleotide") refers to a molecule comprised of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). Sometimes, in a double-stranded form, it can comprise or include a "regulatory element" according to the present invention, as the term is defined herein. The term "oligonucleotide" or "DNA" can be found in linear DNA molecules or fragments, viruses, plasmids, vectors, chromosomes or synthetically derived DNA. As used herein, particular double-stranded DNA sequences may be described according to the normal convention of giving only the sequence in the 5' to 3' direction. Of course, as very well-known, DNA molecules or sequences are often in single stranded form.

"Nucleic acid hybridization" refers generally to the hybridization of two single-stranded nucleic acid molecules having

- complementary base sequences, which under appropriate conditions will form a thermodynamically favored double-stranded structure. Examples of hybridization conditions can be found in the two laboratory manuals referred to above (Sambrook et al., 1989, *supra* and Ausubel et al., 1989, *supra*) and are commonly known in the art. In the case of a hybridization to a nitrocellulose filter, as for example in the well known Southern blotting procedure, a nitrocellulose filter can be incubated overnight at 65°C with a labeled probe in a solution containing 50% formamide, high salt (5 x SSC or 5 x SSPE), 5 x Denhardt's solution, 1% SDS, and 100 µg/ml denatured carrier DNA (i.e. salmon sperm DNA). The non-specifically binding probe can then be washed off the filter by several washes in 0.2 x SSC/0.1% SDS at a temperature which is selected in view of the desired stringency: room temperature (low stringency), 42°C (moderate stringency) or 65°C (high stringency). The selected temperature is based on the melting temperature (T_m) of the DNA hybrid. Of course, RNA-DNA hybrids can also be formed and detected. In such cases, the conditions of hybridization and washing can be adapted according to well known methods by the person of ordinary skill. Stringent conditions will be preferably used (Sambrook et al., 1989, *supra*).
- Probes of the invention can be utilized with naturally occurring sugar-phosphate backbones as well as modified backbones including phosphorothioates, dithionates, alkyl phosphonates and “-nucleotides and the like. Modified sugar-phosphate backbones are generally taught by Miller, 1988, Ann. Reports Med. Chem. 23:295 and Moran et al., 1987, Nucleic Acids Res., 14:5019. Probes of the invention can be constructed of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), and preferably of DNA.

The types of detection methods in which probes can be used include Southern blots (DNA detection), dot or slot blots (DNA,

RNA), and Northern blots (RNA detection). Although less preferred, labeled proteins could also be used to detect a particular nucleic acid sequence to which it binds. More recently, PNAs have been described (Nielsen et al. 1999, Current Opin. Biotechnol. 10:71-75). PNAs could also be used to detect the polymorphisms of the present invention. Other detection methods include kits containing probes on a dipstick setup and the like.

Although the present invention is not specifically dependent on the use of a label for the detection of a particular nucleic acid sequence, such a label might be beneficial, by increasing the sensitivity of the detection. Furthermore, it enables automation. Probes can be labeled according to numerous well known methods (Sambrook et al., 1989, supra). Non-limiting examples of labels include ^3H , ^{14}C , ^{32}P , and ^{35}S . Non-limiting examples of detectable markers include ligands, fluorophores, chemiluminescent agents, enzymes, and antibodies. Other detectable markers for use with probes, which can enable an increase in sensitivity of the method of the invention, include biotin and radionucleotides. It will become evident to the person of ordinary skill that the choice of a particular label dictates the manner in which it is bound to the probe.

As commonly known, radioactive nucleotides can be incorporated into probes of the invention by several methods. Non-limiting examples thereof include kinasing the 5' ends of the probes using gamma ^{32}P ATP and polynucleotide kinase, using the Klenow fragment of Pol I of *E. coli* in the presence of radioactive dNTP (i.e. uniformly labeled DNA probe using random oligonucleotide primers in low-melt gels), using the SP6/T7 system to transcribe a DNA segment in the presence of one or more radioactive NTP, and the like.

As used herein, "oligonucleotides" or "oligos" define a molecule having two or more nucleotides (ribo or deoxyribonucleotides). The size of the oligo will be dictated by the particular situation and ultimately on the particular use thereof and adapted accordingly by the person of ordinary skill. An oligonucleotide can be synthesised chemically or derived by cloning according to well known methods.

As used herein, a "primer" defines an oligonucleotide which is capable of annealing to a target sequence, thereby creating a double stranded region which can serve as an initiation point for nucleic acid synthesis under suitable conditions.

Amplification of a selected, or target, nucleic acid sequence may be carried out by a number of suitable methods. See generally Kwoh et al., 1990, Am. Biotechnol. Lab. 8:14-25. Numerous amplification techniques have been described and can be readily adapted to suit particular needs of a person of ordinary skill. Non-limiting examples of amplification techniques include polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), transcription-based amplification, the Q β replicase system and NASBA (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 1989, *supra*). Preferably, amplification will be carried out using PCR.

Polymerase chain reaction (PCR) is carried out in accordance with known techniques. See, e.g., U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; and 4,965,188 (the disclosures of all three U.S. Patent are incorporated herein by reference). In general, PCR involves, a treatment of a nucleic acid sample (e.g., in the presence of a heat stable DNA polymerase) under hybridizing conditions, with one oligonucleotide primer for each strand of the specific sequence to be detected. An

extension product of each primer which is synthesized is complementary to each of the two nucleic acid strands, with the primers sufficiently complementary to each strand of the specific sequence to hybridize therewith. The extension product synthesized from each primer can also
 5 serve as a template for further synthesis of extension products using the same primers. Following a sufficient number of rounds of synthesis of extension products, the sample is analysed to assess whether the sequence or sequences to be detected are present. Detection of the amplified sequence may be carried out by visualization following EtBr
 10 staining of the DNA following gel electrophores, or using a detectable label in accordance with known techniques, and the like. For a review on PCR techniques (see PCR Protocols, A Guide to Methods and Amplifications, Michael et al. Eds, Acad. Press, 1990).

Ligase chain reaction (LCR) is carried out in
 15 accordance with known techniques (Weiss, 1991, Science 254:1292). Adaptation of the protocol to meet the desired needs can be carried out by a person of ordinary skill. Strand displacement amplification (SDA) is also carried out in accordance with known techniques or adaptations thereof to meet the particular needs (Walker et al., 1992, Proc. Natl. Acad. Sci. USA
 20 89:392-396; and *ibid.*, 1992, Nucleic Acids Res. 20:1691-1696).

As used herein, the term "gene" is well known in the art and relates to a nucleic acid sequence defining a single protein or polypeptide. A "structural gene" defines a DNA sequence which is transcribed into RNA and translated into a protein having a specific amino
 25 acid sequence thereby giving rise to a specific polypeptide or protein. It will be readily recognized by the person of ordinary skill, that the nucleic acid sequence of the present invention can be incorporated into any of numerous established kit formats which are well known in the art.

A “heterologous” (i.e. a heterologous gene) region of a DNA molecule is a subsegment of DNA within a larger segment that is not found in association therewith in nature. The term “heterologous” can be similarly used to define two polypeptidic segments not joined together in nature. Non-limiting examples of heterologous genes include reporter genes such as luciferase, chloramphenicol acetyl transferase, β -galactosidase, and the like which can be juxtaposed or joined to heterologous control regions or to heterologous polypeptides.

The term “vector” is commonly known in the art and defines a plasmid DNA, phage DNA, viral DNA and the like, which can serve as a DNA vehicle into which DNA of the present invention can be cloned. Numerous types of vectors exist and are well known in the art.

The term “expression” defines the process by which a gene is transcribed into mRNA (transcription), the mRNA is then being translated (translation) into one polypeptide (or protein) or more.

The terminology “expression vector” defines a vector or vehicle as described above but designed to enable the expression of an inserted sequence following transformation into a host. The cloned gene (inserted sequence) is usually placed under the control of control element sequences such as promoter sequences. The placing of a cloned gene under such control sequences is often referred to as being operably linked to control elements or sequences.

Operably linked sequences may also include two segments that are transcribed onto the same RNA transcript. Thus, two sequences, such as a promoter and a “reporter sequence” are operably linked if transcription commencing in the promoter will produce an RNA transcript of the reporter sequence. In order to be “operably linked” it is not necessary that two sequences be immediately adjacent to one another.

Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a prokaryotic or eukaryotic host or both (shuttle vectors) and can additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

Prokaryotic expressions are useful for the preparation of large quantities of the protein encoded by the DNA sequence of interest. This protein can be purified according to standard protocols that take advantage of the intrinsic properties thereof, such as size and charge (i.e. SDS gel electrophoresis, gel filtration, centrifugation, ion exchange chromatography...). In addition, the protein of interest can be purified via affinity chromatography using polyclonal or monoclonal antibodies. The purified protein can be used for therapeutic applications.

The DNA construct can be a vector comprising a promoter that is operably linked to an oligonucleotide sequence of the present invention, which is in turn, operably linked to a heterologous gene, such as the gene for the luciferase reporter molecule. "Promoter" refers to a DNA regulatory region capable of binding directly or indirectly to RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of the present invention, the promoter is bound at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter will be found a transcription initiation site (conveniently defined by mapping with S1 nuclease), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain "TATA" boxes and "CCAT" boxes. Prokaryotic promoters

contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

In accordance with one embodiment of the present invention, an expression vector can be constructed to assess the functionality of specific alleles of the SCN1A, SCN2A and SCN3A sodium channels. Non-limiting examples of such expression vectors include a vector comprising the nucleic acid sequence encoding one of the sodium channels (or part thereof) according to the present invention. These vectors can be transfected in cells. The sequences of the alpha subunit of the sodium channels in accordance with the present invention and their structure-function relationship could be assessed by a number of methods known to the skilled artisan. One non-limiting example includes the use of cells expressing the β -1 and β -2 subunits and the sequence of an alpha subunit in accordance with the present invention. For example, an alpha subunit having a mutation, which is linked to epilepsy, could be compared to a sequence devoid of that mutation, as a control. In such cells, the functionality of the sodium channel could be tested as known to the skilled artisan and these cells could be used to screen for agents which could modulate the activity of the sodium channel. For example, agents could be tested and selected, which would reduce the hyperexcitability state of the sodium channel (e.g. their reduction in fast inactivation). Agents known to the person of ordinary skill as affecting other sodium channels could be tested, for example, separately or in batches. Of course, it will be understood that the SCN1A, SCN2A and/or SCN3A genes expressed by these cells can be modified at will (e.g. by *in vitro* mutagenesis or the like).

As used herein, the designation "functional derivative" denotes, in the context of a functional derivative of a sequence whether a nucleic acid or amino acid sequence, a molecule that retains a biological activity (either function or structural; e.g. sodium channel function or

structure) that is substantially similar to that of the original sequence. This functional derivative or equivalent may be a natural derivative or may be prepared synthetically. Such derivatives include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, 5 provided that the biological activity of the protein is conserved. The same applies to derivatives of nucleic acid sequences which can have substitutions, deletions, or additions of one or more nucleotides, provided that the biological activity of the sequence is generally maintained. When relating to a protein sequence, the substituting amino acid generally has 10 chemico-physical properties which are similar to that of the substituted amino acid. The similar chemico-physical properties include, similarities in charge, bulkiness, hydrophobicity, hydrophylicity and the like. The term "functional derivatives" is intended to include "fragments", "segments", "variants", "analogs" or "chemical derivatives" of the subject matter of the 15 present invention. The genetic code, the chemico-physical characteristics of amino acids and teachings relating to conservative vs. non-conservative mutations are well-known in the art. Non-limiting examples of textbooks teaching such information are Stryer, Biochemistry, 3rd ed.; and Lehninger, Biochemistry, 3rd ed. The functional derivatives of the 20 present invention can be synthesized chemically or produced through recombinant DNA technology. all these methods are well known in the art.

The term "variant" refers herein to a protein or nucleic acid molecule which is substantially similar in structure and biological activity to the protein or nucleic acid of the present invention.

25 As used herein, "chemical derivatives" is meant to cover additional chemical moieties not normally part of the subject matter of the invention. Such moieties could affect the physico-chemical characteristic of the derivative (i.e. solubility, absorption, half life, decrease of toxicity and the like). Such moieties are exemplified in

Remington's Pharmaceutical Sciences (1980). Methods of coupling these chemical-physical moieties to a polypeptide or nucleic acid sequence are well known in the art.

5 The term "allele" defines an alternative form of a gene which occupies a given locus on a chromosome.

As commonly known, a "mutation" is a detectable change in the genetic material which can be transmitted to a daughter cell. As well known, a mutation can be, for example, a detectable change in one or more deoxyribonucleotide. For example, nucleotides can be
10 added, deleted, substituted for, inverted, or transposed to a new position. Spontaneous mutations and experimentally induced mutations exist. The result of a mutations of nucleic acid molecule is a mutant nucleic acid molecule. A mutant polypeptide can be encoded from this mutant nucleic acid molecule.

15 As used herein, the term "purified" refers to a molecule having been separated from a cellular component. Thus, for example, a "purified protein" has been purified to a level not found in nature. A "substantially pure" molecule is a molecule that is lacking in all other cellular components.

20 As used herein, "SCNA biological activity" refers to any detectable biological activity of SCN1A, SCN2A or SCN3A gene or protein (herein sometimes collectively called SCNA genes or SCNA proteins). This includes any physiological function attributable to an SCNA gene or protein. It can include the specific biological activity of SCNA proteins
25 which is efflux of sodium or related ions. This includes measurement of channel properties such as, but not limited to: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization necessary to open the channels, 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open

at the resting membrane potential; and 3) the time course of inactivation.

At a larger scale, SCNA biological activity includes transmission of impulses through cells, wherein changes in transmission characteristics caused by modulators of SCNA proteins can be identified. Non-limiting

5 examples of such measurements of these biological activities may be made directly or indirectly, such as through the transient accumulation of ions in a cell, dynamics of membrane depolarization, etc. SCNA biological activity is not limited, however, to these most important biological activities herein identified. Biological activities may also include simple binding or
10 pKa analysis of SCNA with compounds, substrates, interacting proteins, and the like. For example, by measuring the effect of a test compound on its ability to increase or inhibit such SCNA binding or interaction is measuring a biological activity of SCNA according to this invention. SCNA biological activity includes any standard biochemical measurement of
15 SCNA such as conformational changes, phosphorylation status or any other feature of the protein that can be measured with techniques known in the art. Finally, SCNA biological activity also includes activities related to SCNA gene transcription or translation, or any biological activities of such transcripts or translation products.

20 As used herein, the terms "molecule", "compound", "agent" or "ligand" are used interchangeably and broadly to refer to natural, synthetic or semi-synthetic molecules or compounds. The term "molecule" therefore denotes for example chemicals, macromolecules, cell or tissue extracts (from plants or animals) and the like. Non limiting
25 examples of molecules include nucleic acid molecules, peptides, ligands (including, for example, antibodies and carbohydrates) and pharmaceutical agents. The agents can be selected and screened by a variety of means including random screening, rational selection and by rational design using for example protein or ligand modelling methods

such as computer modelling. The terms “rationally selected” or “rationally designed” are meant to define compounds which have been chosen based on the configuration of the interacting domains of the present invention. As will be understood by the person of ordinary skill, 5 macromolecules having non-naturally occurring modifications are also within the scope of the term “molecule”. For example, peptidomimetics, well known in the pharmaceutical industry and generally referred to as peptide analogs can be generated by modelling as mentioned above. Similarly, in a preferred embodiment, the polypeptides of the present 10 invention are modified to enhance their stability. It should be understood that in most cases this modification should not alter the biological activity of the protein. The molecules identified in accordance with the teachings of the present invention have a therapeutic value in diseases or conditions in which sodium transport through the sodium channels is compromised by a mutation (or combination thereof) in one of the genes identified in 15 accordance with the present invention. Alternatively, the molecules identified in accordance with the teachings of the present invention find utility in the development of compounds which can modulate the activity of the alpha subunit sodium channels and/or the action potential in nerve 20 cells and muscles cells (e.g. restore the fast inactivation of the sodium channel to normal levels).

As used herein, agonists and antagonists also include potentiators of known compounds with such agonist or antagonist properties. In one embodiment, modulators of the fast inactivation of the 25 sodium channel in accordance with the present invention can be identified and selected by contacting the indicator cell with a compound or mixture or library of molecules for a fixed period of time.

As used herein the recitation “indicator cells” refers to cells that express at least one sodium channel α subunit (SCNA)

according to the present invention. As alluded to above, such indicator cells can be used in the screening assays of the present invention. In certain embodiments, the indicator cells have been engineered so as to express a chosen derivative, fragment, homolog, or mutant of the combination of genotypes of the present invention. The cells can be yeast cells or higher eukaryotic cells such as mammalian cells. In one particular embodiment, the indicator cell would be a yeast cell harboring vectors enabling the use of the two hybrid system technology, as well known in the art (Ausubel et al., 1994, *supra*) and can be used to test a compound or a library thereof. In another embodiment, the *cis-trans* assay as described in USP 4,981,784, can be adapted and used in accordance with the present invention. Such an indicator cell could be used to rapidly screen at high-throughput a vast array of test molecules. In a particular embodiment, the reporter gene is luciferase or β -Gal.

It shall be understood that the "*in vivo*" experimental model can also be used to carry out an "*in vitro*" assay. For example, cellular extracts from the indicator cells can be prepared and used in an "*in vitro*" test. A non-limiting example thereof include binding assays.

In some embodiments, it might be beneficial to express a fusion protein. The design of constructs therefor and the expression and production of fusion proteins and are well known in the art (Sambrook et al., 1989, *supra*; and Ausubel et al., 1994, *supra*).

Non-limiting examples of such fusion proteins include hemagglutinin fusions and Gluthione-S-transferase (GST) fusions and Maltose binding protein (MBP) fusions. In certain embodiments, it might be beneficial to introduce a protease cleavage site between the two polypeptide sequences which have been fused. Such protease cleavage sites between two heterologously fused polypeptides are well known in the art.

In certain embodiments, it might also be beneficial to fuse the protein of the present invention to signal peptide sequences enabling a secretion of the fusion protein from the host cell. Signal peptides from diverse organisms are well known in the art. Bacterial
5 OmpA and yeast Suc2 are two non-limiting examples of proteins containing signal sequences. In certain embodiments, it might also be beneficial to introduce a linker (commonly known) between the interaction domain and the heterologous polypeptide portion. Such fusion protein find utility in the assays of the present invention as well as for purification
10 purposes, detection purposes and the like.

For certainty, the sequences and polypeptides useful to practice the invention include without being limited thereto mutants, homologs, subtypes, alleles and the like. It shall be understood that generally, the sequences of the present invention should encode a
15 functional (albeit defective) alpha subunit of sodium channels (SCNA). It will be clear to the person of ordinary skill that whether the SCNA sequence of the present invention, variant, derivative, or fragment thereof retains its function, can be determined by using the teachings and assays of the present invention and the general teachings of the art.

20 It should be understood that the SCNA protein of the present invention can be modified, for example by *in vitro* mutagenesis, to dissect the structure-function relationship thereof and permit a better design and identification of modulating compounds. However, some derivative or analogs having lost their biological function may still find
25 utility, for example for raising antibodies. These antibodies could be used for detection or purification purposes. In addition, these antibodies could also act as competitive or non-competitive inhibitor and be found to be modulators of the activity of the SCNA proteins of the present invention.

A host cell or indicator cell has been "transfected" by exogenous or heterologous DNA (e.g. a DNA construct) when such DNA has been introduced inside the cell. The transfecting DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transfecting DNA may be maintained on an episomal element such as a plasmid. With respect to eukaryotic cells, a stably transfected cell is one in which the transfecting DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transfecting DNA. Transfection methods are well known in the art (Sambrook et al., 1989, *supra*; Ausubel et al., 1994 *supra*). The use of a mammalian cell as indicator can provide the advantage of furnishing an intermediate factor, which permits for example the interaction of two polypeptides which are tested, that might not be present in lower eukaryotes or prokaryotes. It will be understood that extracts from mammalian cells for example could be used in certain embodiments, to compensate for the lack of certain factors.

In general, techniques for preparing antibodies (including monoclonal antibodies and hybridomas) and for detecting antigens using antibodies are well known in the art (Campbell, 1984, In "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", Elsevier Science Publisher, Amsterdam, The Netherlands) and in Harlow et al., 1988 (in: Antibody-A Laboratory Manual, CSH Laboratories). The present invention also provides polyclonal, monoclonal antibodies, or humanized versions thereof, chimeric antibodies and the like which inhibit or neutralize their respective interaction domains and/or are specific thereto.

From the specification and appended claims, the term therapeutic agent should be taken in a broad sense so as to also include a combination of at least two such therapeutic agents. Further, the DNA segments or proteins according to the present invention could be introduced into individuals in a number of ways. For example, cells can be isolated from the afflicted individual, transformed with a DNA construct according to the invention and reintroduced to the afflicted individual in a number of ways. Alternatively, the DNA construct can be administered directly to the afflicted individual. The DNA construct can also be delivered through a vehicle such as a liposome, which can be designed to be targeted to a specific cell type, and engineered to be administered through different routes.

For administration to humans, the prescribing medical professional will ultimately determine the appropriate form and dosage for a given patient, and this can be expected to vary according to the chosen therapeutic regimen (i.e. DNA construct, protein, cells), the response and condition of the patient as well as the severity of the disease.

Composition within the scope of the present invention should contain the active agent (i.e. molecule, hormone) in an amount effective to achieve the desired therapeutic effect while avoiding adverse side effects. Typically, the nucleic acids in accordance with the present invention can be administered to mammals (i.e. humans) in doses ranging from 0.005 to 1 mg per kg of body weight per day of the mammal which is treated. Pharmaceutically acceptable preparations and salts of the active agent are within the scope of the present invention and are well known in the art (Remington's Pharmaceutical Science, 16th Ed., Mack Ed.). For the administration of polypeptides, antagonists, agonists and the like, the amount administered should be chosen so as to avoid adverse side effects. The dosage will be adapted by the clinician in accordance with

conventional factors such as the extent of the disease and different parameters from the patient. Typically, 0.001 to 50 mg/kg/day will be administered to the mammal.

The present invention also relates to a kit for
 5 diagnosing and/or prognosing epilepsy, and/or predicting response to a medication comprising an assessment of a genotype at SCNA loci of the present invention (or loci in linkage disequilibrium therewith) using a nucleic acid fragment, a protein or a ligand, a restriction enzyme or the like, in accordance with the present invention. For example, a
 10 compartmentalized kit in accordance with the present invention includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of
 15 each container can be added in a quantitative fashion from one compartment to another. Such containers will include in one particular embodiment a container which will accept the test sample (DNA protein or cells), a container which contains the primers used in the assay, containers which contain enzymes, containers which contain wash
 20 reagents, and containers which contain the reagents used to detect the extension products.

BRIEF DESCRIPTION OF THE DRAWINGS

Having thus generally described the invention,
 25 reference will now be made to the accompanying drawings, showing by way of illustration a preferred embodiment thereof, and in which:

Figure 1 shows the IGE candidate region on ch 2q23-q31. Order and distance between markers are according to Gyapay et al., 1994.

Figure 2 shows the PCR primers used for genomic PCR-SSCP of SCN1A;

Figure 3 shows the sequence of the SCN1A mutations found in epilepsy patients;

5 Figure 4 shows the PCR primers used for genomic PCR-SSCP of SCN2A;

Figure 5 shows the mutation found in epilepsy patients in SCN2A;

10 Figure 6 shows the PCR primers used for genomic PCR-SSCP of SCN3A; and

Figure 7 shows the mutation found in epilepsy patients in SCN3A.

Sequences are also shown in the Sequence Listing. For example, SEQ ID NO.:1 shows the nucleic acid sequence of the adult form of SCN1A; SEQ ID NO.:2 shows the nucleic acid sequence of the
 15 neonatal form of SCN1A; SEQ ID NO.:3 shows the protein sequence of the adult form of SCN1A; SEQ ID NO.:4 shows the protein sequence of the neonatal form of SCN1A; SEQ ID NOS.:5-32 show the genomic sequence of SCN1A; SEQ ID NO.:33 shows the cDNA sequence of the
 20 adult form of SCN2A; SEQ ID NO.:34 shows the cDNA sequence of the neonatal form of SCN2A; SEQ ID NO.:35 shows the protein sequence of the adult form of SCN2A; SEQ ID NO.:36 shows the protein sequence of the neonatal form of SCN2A; SEQ ID NOS.:37-64 show the genomic sequence of SCN2A; SEQ ID NO.:65 shows the cDNA sequence of the
 25 adult form of SCN3A; SEQ ID NO.:66 shows the cDNA sequence of the neonatal form of SCN3A; SEQ ID NO.:67 shows the protein sequence of the adult form of SCN3A; SEQ ID NO.:68 shows the protein sequence of the neonatal form of SCN3A; and SEQ ID NOS.:69-98 show the genomic sequence of SCN3A;

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawing which is exemplary and should not be interpreted as limiting the scope of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Epilepsy is one of the most common neurological conditions, affecting 1-2% of the general population. Familial aggregation studies have shown an increased risk for epilepsy in relatives of probands with different types of epilepsy, and especially for the idiopathic generalized epilepsies (IGEs). The epilepsy genes identified to date account for a very small proportion of all the epilepsies. In addition, they have been identified in rare syndromes where the pattern of inheritance was clearly Mendelian. This is not the case for the vast majority of epileptic patients, however, where the pattern of inheritance is not compatible with a simple Mendelian model. In fact, most authors consider epilepsy to be the result of a combination of many different genetic and environmental factors, features of a complex trait. While the pattern of inheritance is not mendelian, sporadic IGE cases may be caused by specific mutations in the same genes. Based on this assumption, a large cohort of IGE patients was tested for mutation in the SCN1A genes.

In order to localize the gene causing epilepsy in a large family segregating an autosomal dominant form of IGE, 41 family members, including 21 affected individuals, were genotyped. A detailed clinical description of this family has been reported elsewhere (Scheffer and Berkovic 1997). The majority of patients in this family present a benign epilepsy syndrome occurring in childhood and characterized by frequent generalized tonic-clonic seizures not always associated with fever: a syndrome called febrile seizures plus (FS+). However, several

- patients presented other types of generalized seizures (GTCS) as well, such as myoclonic seizures and absences (Scheffer and Berkovic 1997). Mean age at onset was 2.2 years and offset was 11.7 years. Neurological examination and intellect were normal in all individuals except one, who
- 5 had moderate intellectual disability. EEG recordings were normal in most patients. However, in three individuals generalized epileptiform activity was found and four patients had mild or moderate diffuse background slowing. Table 1 shows the different types of seizures found in the 21 patients included in this study.

Table 1. Different types of generalized seizures found in the 21 patients included in the linkage analysis.

Type of seizures	n
Febrile convulsions alone	9
GTCSs ^a + absence seizures	4
GTCSs + myoclonic seizures	1
GTCSs + atonic seizures	1
Solitary afebrile GTCS	1
Secondary epilepsy + mental retardation	1
Unwitnessed events	4

^a GTCS: generalized tonic clonic seizure

5

A genome wide search examining 190 markers identified linkage of IGE to chromosome (ch) 2 based on an initial positive lod score for marker D2S294 ($Z=4.4$, ($=0$)). A total of 24 markers were tested on ch 2q in order to define the smallest IGE candidate region. Table 2 shows the two-point lod scores for 17 markers spanning the IGE candidate region. The highest lod score ($Z_{\max}=5.29$; ($=0$)) was obtained with marker D2S324. Critical recombination events mapped the IGE gene to a 29cM region flanked by markers D2S156 and D2S311, assigning the IGE locus to ch 2q23-q31 (Figure 1). Although the relationship of FS+ with other IGE phenotypes remains unclear, the observation that in this family, several affected individuals have different types of generalized seizures, suggests that seizure predisposition determined by the ch 2q-IGE gene could be modified by other genes and/or environmental factors, to produce different seizure types.

20

Table 2. Two-point lod-scores for 17 markers localized on ch 2q23-q31.

Locus	Recombination fractions							Zmax	max
	0	0.05	0.1	0.15	0.2	0.3	0.4		
D2S142	0.99	1.94	1.97	1.85	1.68	1.22	0.66	1.98	0.078
D2S284	1.3	1.18	1.06	0.94	0.82	0.57	0.3	1.3	0
D2S306	1.9	2.82	2.74	2.52	2.25	1.6	0.85	2.82	0.057
D2S156	2.15	3.05	2.96	2.73	2.43	1.73	0.93	3.05	0.056
D2S354	4.72	4.26	3.82	3.4	2.97	2.1	1.13	4.72	0
D2S111	5.15	4.71	4.26	3.78	3.29	2.26	1.17	5.15	0
D2S124	3.5	3.2	2.89	2.58	2.26	1.58	0.84	3.5	0
D2S382	4.31	3.93	3.54	3.14	2.74	1.91	1.02	4.31	0
D2S399	0.48	0.4	0.33	0.27	0.22	0.14	0.08	0.48	0
D2S294	4.4	4.04	3.65	3.25	2.84	2	1.07	4.4	0
D2S335	4.76	4.32	3.91	3.51	3.1	2.22	1.21	4.76	0
D2S333	1.42	1.23	1.04	0.87	0.72	0.45	0.22	1.4	0
D2S324	5.29	4.72	4.16	3.63	3.13	2.15	1.14	5.29	0
D2S384	3.85	3.52	3.17	2.82	2.45	1.69	0.89	3.85	0
D2S152	1.9	1.7	1.52	1.36	1.2	0.87	0.48	1.9	0
D2S311	-0.81	1.62	1.66	1.58	1.46	1.11	0.63	1.66	0.085
D2S155	-5.21	0.57	1.12	1.29	1.29	1.04	0.59	1.3	0.17

Haplotypes using 17 markers spanning the IGE candidate region were constructed (data not shown). The centromeric boundary was defined by a recombination event between the markers D2S156 and D2S354; whereas a recombination between the markers D2S152 and D2S311 set the telomeric boundary. These critical recombination events localized the IGE gene to a 29cM region flanked by markers D2S156 and D2S311 (Figure 1).

Over the last four decades, family studies provided two important pieces of evidence supporting the role of genetic factors in determining susceptibility to seizures: 1) familial aggregation studies have shown evidence for an increased risk for epilepsy in relatives of probands with different types of epilepsy. In two studies standardized morbidity ratios for unprovoked seizures in relatives of individuals with idiopathic childhood-onset epilepsy varied from 2.5 to 3.4 in siblings and 6.7 in offspring (Anneger et al. 1982; Ottman et al. 1989); and 2) the presence of higher concordance rates for epilepsy in monozygotic than in dizygotic twins. Different studies showed concordance rates varying from 54 to 11 % in monozygotic twins and 10 to 5% in dizygotic pairs (Inouye 1960; Lennox, 1960; Harvald and Hauge 1965; Corey et al. 1991; Silanpaa et al 1991).

It is now generally accepted that seizure susceptibility probably reflects complex interactions of multiple factors affecting neuronal excitability and that most common genetic epilepsies display familial aggregation patterns that are not explained by segregation of a single autosomal gene (Andermann 1982; Ottman et al. 1995). This of course significantly makes more complex one's ability to isolate genes which predispose or induce epilepsy. However, some specific epileptic syndromes, which aggregate in families, may result from definable monogenic abnormalities. These families present a unique opportunity to

rapidly map genes that play a role in determining predisposition to seizures.

To date, there are a total of six loci (Greenberg et al. 1988; Leppert et al 1989; Lewis et al. 1993; Elmslie et al. 1997; Guipponi et al. 1997; Wallace et al. 1998), for which three genes have been identified in specific IGE syndromes (Bievert et al. 1998; Singh et al. 1998; Wallace et al. 1998). Interestingly, all three genes are ion channels, including a mutation found in the Na⁺-channel (1 in a Tasmania family with febrile seizures and generalized epilepsy (Wallace et al. 1998). While the candidate interval identified in our kindred remains large, a number of interesting genes map to the region. These include a cluster of Na⁺ channel genes and K⁺ channel genes (electronic data base search), as well as the GAD1 gene, which encodes for glutamate decarboxylase, an enzyme involved in the syntheses of γ -aminobutyric acid (GABA) (Bu and Tobin 1994). GABA is one of the major neurotransmitters involved in synaptic inhibition in the central nervous system (Barnard et al. 1987). However, the large size of the candidate interval will require further refinement of the locus prior to the identification of the gene responsible for IGE in the kindred studied herein.

Fifty-three % (9/17) of affected individuals in the large IGE family described herein, who had their seizures classified, had only febrile convulsions. However, 41 % of patients (7/17) presented with different types of generalized seizures. These findings may indicate that, although the predisposition to IGE in this family is determined by a single gene localized on ch2q23-q31, the different types of generalized seizures occurring in the same family may have resulted from interactions among genetic and/or environmental modifiers.

In conclusion, a locus for IGE was mapped on ch 2q23-q31. This locus seems to be associated with a specific IGE syndrome, FS

+. However, the relationship of FS+ with other IGE phenotypes, and the role of the ch 2q locus in other FS+ families and in other forms of IGE are still undetermined.

Having identified a locus for IGE on chromosome 2q23-q31, it was next verified whether mutations and/or polymorphisms could be linked to epilepsy. Public data bases were screened to identify potential genes in that chromosome region. The blasts of the data bases were also oriented to identify more specifically, membrane channels since seizures in mice and human are known to be associated with membrane channels. Having identified membrane channel coding sequences or parts thereof by the computer searches, the candidate genes, potentially involved in epilepsy, had to be validated as susceptibility genes for the disease. Two approaches were used. The first one was to test the candidate genes for mutations in a family comprising members having the disease (data not shown). The second approach was as follows. Since it is known that epilepsy results from a lower seizure threshold, and that generalized epilepsy results, in many instances, from a generalized lowering of the seizure threshold, the following hypothesis was formulated. The gene which results in epilepsy in the large family (that enabled the focusing chromosome 2q23-q31) should have other, less severe, mutations that would cause epilepsy in people who have only a weak family history of epilepsy. The sodium channel genes were chosen because they are involved in key electrical functions and could thus be good candidates. To formally test the hypothesis, many (60 to 70) unrelated cases of epilepsy were tested for mutations in these candidate genes. Surprisingly, mutations were found in all three candidate genes.

In order to assess whether mutations/polymorphisms could be identified and correlated to epilepsy, a panel of 70 to 80 epileptic patients (IGE) were tested for mutations in SCN1A, SCN2A and SCN3A,

using Single-strand conformation polymorphism (SSCP). SSCP analysis enables the detection of mutations as small as single-base substitutions. Indeed, such substitutions, by altering the conformations of single-strand DNA molecules, affect the electrophoretic mobilities thereof in non-denaturing gels. Thus, one can distinguish among sequences by comparing the mobilities of wild type (wt), mutant DNA, or different alleles of a given locus. The identification of single base substitutions of genes using SSCP is well known in the art, and numerous protocols are available therefor. A non-limiting example thereof includes fluorescence-based SSCP analysis, following PCR carried out using fluorescent-labeled primers specific for the DNA regions one wishes to amplify.

Upon the identification of differences between normal and epileptic mobilities for one of the SCNA loci of the present invention, the amplified fragments were sequenced and the nucleic acid sequences between a normal patient and an epileptic patient (IGE) compared. This comparison enabled the identification of mutations in SCN1A, SCN2A, and SCN3A. To assess, whether this difference in sequence or mutation was significantly associated with the disease, SSCP analysis was performed once again using a large cohort of normal patients. This analysis enabled to show that the mutations identified by SSCP and confirmed by sequence analysis were not present in the large cohort of normal patients tested, thereby showing that the mutations identified correlated with IGE, for the population tested.

Taken together, these results show that SCN1A, SCN2A and SCN3A are validated genes associated with epilepsy and more specifically with IGE.

This invention now establishes, for the first time, that SCN1A, SCN2A, and SCN3A, is directly responsible for idiopathic generalized epilepsy (IGE) in certain human populations. Further, this

discovery suggests that compounds which modulate the activity of SCN1A, SCN2A and SCN3A may have application far beyond the small groups of families with IGE, and may have applicability for treating many or all forms of epilepsy and related neurological disorders. It is therefore an object of this invention to provide screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. This invention also claims those compounds, the use of these compounds in treating epilepsy and related neurological disorders, and any use of any compounds identified using such a screening assay in treating epilepsy and related neurological disorders.

Generally, high throughput screens for one or more SCN1A, SCN2A or SCN3A (herein collectively called SCNA) sodium channels modulators i.e. candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) may be based on assays which measure biological activity of SCNA. The invention therefore provides a method (also referred to herein as a "screening assay") for identifying modulators, which have a stimulatory or inhibitory effect on, for example, SCNA biological activity or expression, or which bind to or interact with SCNA proteins, or which have a stimulatory or inhibitory effect on, for example, the expression or activity of SCNA interacting proteins (targets) or substrates.

Examples of methods available for cell-based assays and instrumentation for screening ion-channel targets are described in the review by Gonzalez et al. (Drug Discov. Today 4:431-439, 1999), and high-throughput screens for ion-channel drugs are described in review by Denyer et al. (Drug Discov. Today 3:323-332, 1998). Such assays include efflux of sodium or related ions that can be measured in a cell line (recombinant or non-recombinant) using fluorescence-based assays using

both sodium indicator dyes and voltage sensing dyes. Preferred assays employ ^{14}C guanidine flux and/or sodium indicator dyes such as SBFI and voltage sensing dyes such as DiBAC. Oxonal dyes such as DiBAC₄ are responsive to membrane depolarization. Hyper-polarization results in removal of the dye from the cell by passive diffusion, while depolarization results in concentration of the dye within the cell.

In one embodiment, the invention provides assays for screening candidate or test compounds which interact with substrates of a SCNA protein or biologically active portion thereof.

In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a SCNA protein or polypeptide or biologically active portion thereof.

In one embodiment, an assay is a cell-based assay in which a cell which expresses a SCNA protein or biologically active portion thereof, either natural or recombinant in origin, is contacted with a test compound and the ability of the test compound to modulate SCNA biological activity, e.g., modulation of sodium efflux activity, or binding to a sodium channel or a portion thereof, or any other measurable biological activity of SCNA is determined. Determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the release of a neurotransmitter or other compound, from a cell which expresses SCNA such as a neuronal cell, e.g. a substantia nigra neuronal cell, or a cardiac cell upon exposure of the test compound to the cell. Furthermore, determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the change in current or the change in release of a neurotransmitter from a cell which expresses SCNA upon exposure to a test compound. Currents in cells can be measured using the patch-clamp technique as

described in the Examples below using the techniques described in, for example, Hamill et al. 1981 *Pfluegers Arch.* 391:85-100. Alternatively, changes in current can be measured by dye based fluorescence assays described below.

Determining the ability of the test compound to modulate binding of SCNA to a substrate can be accomplished, for example, by coupling the SCNA agent or substrate with a radioisotope or enzymatic label such that binding of the SCNA substrate to SCNA can be determined by detecting the labeled SCNA substrate in a complex. For example, compounds (e.g., SCNA agents or substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting radio-emission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase or alkaline phosphatase. In these assays, compounds which inhibit or increase substrate binding to SCNA are useful for the therapeutic objectives of the invention.

It is also within the scope of this invention to determine the ability of a compound (e.g. SCNA substrate) to interact with SCNA without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with SCNA without the labeling of either the compound or the SCNA (McConnell H.M. et al. (1992), Science 257:1906-1912). As used herein, a "microphysiometer" (e.g., Cytosensor™) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and SCNA.

Modulators of SCNA can also be identified through the changes they induce in membrane potential. A suitable instrument for

measuring such changes is the VIPR™ (voltage ion probe reader) from Aurora Biosciences. This instrument works together with a series of voltage-sensing ion probe assays. The probes sense changes in transmembrane electrical potential through a voltage-sensitive FRET mechanism for which the ratio donor fluorescence emission to acceptor fluorescence emission reveals the extent of cell depolarization for both sodium and potassium channels. Depolarization results from transport of a quencher across the membrane and far enough away from a membrane-bound fluorescence emitter to relieve the initial quenching and produce light at the emission wavelength of the emitter. The system follows fluorescence at two wavelengths, both the intensities and ratios change during cell depolarization. The reader permits detection of sub-second, real-time optical signals from living cells in a microplate format. The system is amenable to manual operation for assay development or automation via robots for high-throughput screening.

In another embodiment, the assay is a cell-based assay comprising a contacting of a cell containing a target molecule (e.g. another molecule, substrate or protein that interacts with or binds to SCNA) with a test compound and determining the ability of the test compound to indirectly modulate (e.g. stimulate or inhibit) the biological activity of SCNA by binding or interacting with the target molecule. Determining the ability of the test compound to indirectly modulate the activity of SCNA can be accomplished, for example, by determining the ability of the test compound to bind to or interact with the target molecule and thereby to indirectly modulate SCNA, to modulate sodium efflux, or to modulate other biological activities of SCNA. Determining the ability of the SCNA protein or a biologically active fragment thereof, to bind to or interact with the target molecule can be accomplished by one of the methods described above or known in the art for determining direct binding. In a preferred embodiment, determining the ability of the test

compound's ability to bind to or interact with the target molecule and thereby to modulate the SCNA protein can be accomplished by determining a secondary activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g. intracellular Ca^{2+} , diacylglycerol, IP3, and the like), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target -responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, such as luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter. Alternatively, recombinant cell lines may employ recombinant reporter proteins which respond, either directly or indirectly to sodium efflux or secondary messengers all as known in the art

In yet another embodiment, an assay of the present invention is a cell-free assay in which a SCNA protein or biologically active portion thereof, either naturally occurring or recombinant in origin, is contacted with a test compound and the ability of the test compound to bind to, or otherwise modulate the biological activity of, the SCNA protein or biologically active portion thereof is determined. Preferred biologically active portions of the SCNA proteins to be used in assays of the present invention include fragments which participate in interactions with non-SCNA molecules, (e.g. other channels for sodium, potassium or Ca^{2+} or fragments thereof, or fragments with high surface probability scores for protein-protein or protein-substrate interactions). Binding of the test compound to the SCNA protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the SCNA protein or biologically active portion thereof with a known compound which binds SCNA to form an assay mixture, contacting the assay mixture with a test compound, and determining the

ability of the test compound to interact with a SCNA protein, wherein determining the ability of the test compound to interact with a SCNA protein comprises determining the ability of the test compound to preferentially bind to SCNA or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a SCNA protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the SCNA protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished, for example, by determining the ability of the SCNA protein to bind to a SCNA target molecule by one of the methods described above for determining direct binding. Determining the ability of the SCNA protein to bind to a SCNA target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA, Sjolander, S. and Urbaniczky, C. (1991) Anal. Chem. 63:2338-2345 and Szabo et al. (1995) Curr Opin. Struct. Biol. 5:699-705) As used herein, "BIA" refers to a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g. BIA core). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished by determining the ability of the test compound to modulate the activity of an upstream or downstream effector of a SCNA target molecule. For example, the activity of the test compound on the effector molecule can be determined or the binding of the effector to SCNA can be determined as previously described.

The cell-free assays of the present invention are amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g. a sodium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecylpoly(ethylene glycol ether)n, 3-[(3-cholamidopropyl)dimethylamino]-l-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamino]-2-hydroxy-l-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammnonio-l-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either SCNA or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a SCNA protein or interaction of a SCNA protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes and micro-centrifuge tubes. In one embodiment a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/SCNA fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target

protein or SCNA protein and the mixture incubated under conditions conducive to complex formation (e.g. at physiological conditions for salt and pH). Following incubation the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in

5 the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of SCNA binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices

10 (and well-known in the art) can also be used in the screening assays of the invention. For example, either a SCNA protein or a SCNA target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated SCNA protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques

15 known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with SCNA protein or target molecules but which do not interfere with binding of the SCNA protein to its target molecule can be derivatized to the wells of the plate, and

20 unbound target or SCNA protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST -immobilized complexes, include immunodetection of complexes using antibodies reactive with the SCNA protein or target molecule, as well as enzyme-linked assays which rely on

25 detecting an enzymatic activity associated with the SCNA protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate vesicular traffic and protein transport

in a cell, e.g. a neuronal or cardiac cell using the assays described in for example Komada M. et al. (1999) Genes Dev.13(11):1475-85, and Roth M.G. et al. (1999) Chem. Phys. Lipids. 98(12):141-52.

- In another preferred embodiment candidate, or test
- 5 compounds or agents are tested for their ability to inhibit or stimulate or regulate the phosphorylation state of a SCNA channel protein or portion thereof, or an upstream or downstream target protein, using for example an *in vitro* kinase assay. Briefly, a SCNA target molecule (e.g. an immunoprecipitated sodium channel from a cell line expressing such a
 - 10 molecule), can be incubated with radioactive ATP, e.g., [gamma-32P] - ATP, in a buffer containing MgCl₂ and MnCl₂, e.g., 10 mM MgCl₂ and 5 mM MnCl₂. Following the incubation, the immunoprecipitated SCNA target molecule (e.g. the sodium channel), can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred
 - 15 to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the auto radiograph indicates that the SCNA substrate, e.g., the sodium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the SCNA substrate
 - 20 are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in,
 - 25 for example, Tamaskovic R. et al. (1999) Biol. Chem. 380(5):569-78.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to associate with (e.g. bind) calcium, using for

example, the assays described in Liu L. (1999) *Cell Signal.* 11(5):317-24 and Kawai T. et al. (1999) *Oncogene* 18(23):3471-80.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate chromatin formation in a cell using for example the assays described in Okuwaki M. et al. (1998) *J. Biol. Chem.* 273(51):34511-8 and Miyaji- Yamaguchi M. (1999) *J. Mol. Biol.* 290(2): 547-557.

In yet another preferred embodiment candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cellular proliferation, using for example, the assays described in Baker F.L. et al. (1995) *Cell Prolif.* 28(1):1-15, Cheviron N. et al. (1996) *Cell Prolif.* 29(8):437-46. Hu Z. W. et al. (1999) *J. Pharmacol. Exp. Ther.* 290(1):28-37 and Elliott K. et al. (1999) *Oncogene* 18(24):3564-73.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to regulate its association with the cellular cytoskeleton. Using for example, the assays similar to those described in Gonzalez C. et al. (1998) *Cell Mol. Biol.* 44(7):1117-27 and Chia C.P. et al. (1998) *Exp. Cell Res.* 244(1):340-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. et al. (1985) *J. Biol. Chem.* 260(8):4740-4 and Barker J.L. et al. (1984) *Neurosci. Lett.* 47(3):313-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cytokine signaling in a cell, (e.g., a

neuronal or cardiac cell), the assays described in Nakashima Y. et al. (1999)J: Bone Joint Surg. Am. 81 (5):603-15.

In another embodiment, modulators of SCNA expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of SCNA mRNA or protein in the cell is determined. The level of expression of SCNA mRNA or protein in the presence of the candidate compound is compared to the level of expression of SCNA mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of SCNA expression based on this comparison. For example, when expression of SCNA mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of SCNA mRNA or protein expression. Alternatively, when expression of SCNA mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of SCNA mRNA or protein expression. The level of SCNA mRNA or protein expression in the cells can be determined by methods described herein or other methods known in the art for detecting SCNA mRNA or protein.

The assays described above may be used as initial or primary screens to detect promising lead compounds for further development. Often, lead compounds will be further assessed in additional, different screens. Therefore, this invention also includes secondary SCNA screens which may involve electrophysiological assays utilizing mammalian cell lines expressing the SCNA channels such as patch clamp technology or two electrode voltage clamp and FRET-based voltage sensor. Standard patch clamp assays express wild type and mutant channels in *Xenopus* oocytes, and examine their properties using

voltage-clamp electrophysiological recording. Wild type sodium channels are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds.

- 10 Tertiary screens may involve the study of the identified modulators in rat and mouse models for epilepsy. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an test compound identified as described herein (e.g., a SCNA modulating agent, an
- 15 antisense SCNA nucleic acid molecule, a SCNA-specific antibody, or a SCNA-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent.
- 20 Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment (e.g. treatments of different types of epilepsy or CNS disorders), as described herein.

- The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially
- 25 addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to

peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des. 12: 145, 1997). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in:

- 5 DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994), J. Med. Chem. 37:2678; Cho et al. (1993) Science 261 :1303; Carrell et al. (1994) Angew. Chem, Int. Ed Engl. 33:2059; Carell et al. (1994) Angew. Chem. Jnl. Ed. Engl. 33:2061; and in Gallop et al. (1994). Med Chem. 37:1233.
- 10 Libraries of compounds may be presented in solution (e.g.. Houghten (1992) Biotechniques 13:412-421). or on beads (Lam (1999]) Nature 354:82-84), chips (Fodor (1993) Nature 364:555-556). bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull et al.(1992) Proc Natl Acad Sci USA 89:1865-1869) or on phage (Scott and Smith (
- 15 1990); Science 249:386-390). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91: 11422; Zuckermann et al. (1994), J. Med. Chem. 37:2678; Cho et al. (1993), Science 261 :1303; Carrell et al. (1994)
- 20 Angew. Chem Int. Ed. Engl. 33:2059, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

- In summary, based on the disclosure herein, those skilled in the art can develop SCNA screening assays which are useful for
- 25 identifying compounds which are useful for treating epilepsy and other disorders which relate to potentiation of SCNA expressing cells. The assays of this invention may be developed for low-throughput, high-throughput, or ultra-high throughput screening formats.

The assays of this invention employ either natural or recombinant SCNA protein. Cell fraction or cell free screening assays for modulators of SCNA biological activity can use *in situ*, purified, or purified recombinant SCNA proteins. Cell based assays can employ cells which

5 express SCNA protein naturally, or which contain recombinant SCNA gene constructs, which constructs may optionally include inducible promoter sequences. In all cases, the biological activity of SCNA can be directly or indirectly measured; thus modulators of SCNA biological activity can be identified. The modulators themselves may be further

10 modified by standard combinatorial chemistry techniques to provide improved analogs of the originally identified compounds.

Finally, portions or fragments of the SCNA cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents.

15 For example, these sequences can be used to: (i) map their respective genes on a chromosome and thus, locate gene regions associated with genetic disease (mutations/polymorphisms) related to epilepsy or CNS disorders that involve SCNA directly or indirectly; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic

20 identification of a biological sample.

The present invention is illustrated in further detail by the following non-limiting examples.

EXAMPLE 1

25

Molecular analysis

Genomic DNA was extracted from blood samples (Sambrook et al. 1989) or lymphoblastoid cell lines (Anderson and Gusella 1984) from each individual. A panel of 210 dinucleotide (CA)_n repeat polymorphic markers with high heterozygosity (75%) were chosen

from the 1993-94 Généthon map (Gyapay et al. 1994). Dinucleotide markers were spaced an average of 20 cM from each other throughout the 22 autosomes.

- Genotyping of microsatellite markers was accomplished by polymerase chain reaction (PCR). The reaction mixture was prepared in a total volume of 13 μ l, using 80ng genomic DNA; 1.25 μ l 10x buffer with 1.5mM MgCl₂; 0.65 μ l BSA (2.0mg/ml); 100ng of each oligonucleotide primer; 200mM dCTP, dGTP and dTTP; 25mM dATP; 1.5mCi [35S] dATP; and 0.5units Taq DNA polymerase (Perkin-Elmer).
- Reaction samples were transferred to 96 well plates and were subjected to: 35 cycles of denaturation for 30 seconds at 94°C, annealing for 30 seconds at temperatures varying from 55°C to 57°C depending on the specificity of the oligonucleotide primers, and elongation for 30 seconds at 72°C. PCR reaction products were electrophoresed on 6% denaturing polyacrylamide sequencing gels.

EXAMPLE 2

Genetic analysis

- Two-point linkage analysis was carried out using the MLINK program version 5.1 from the LINKAGE computer package (Lathrop et al. 1984). Precise values for Zmax were calculated with the ILINK program from the same computer package. Lod scores were generated based on an autosomal dominant mode of inheritance, 80% penetrance, disease gene frequency of 1:500 and allele frequencies for all allele markers calculated from the pedigree using the computer program ILINK (Lathrop et al. 1984).

EXAMPLE 3

Mutations in SCN1A in IGE patients

- Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 2. Following PCR, SSCP analysis was performed and mutations in SCN1A were identified as follows (Figure 3):
- (1) Glu1238Asp; normal: GCA TTT GAA GAT ATA; patient R10191 who has an idiopathic generalized epilepsy (IGE): GCA TTT GAC GAT ATA (found in 1 of 70 IGE patients). The mutation is thus a conservative aa change, in the extracellular domain between III-S1 and III-S2. Furthermore, this residue is located at the junction between the TM domain and the extracellular domain. It may thus influence gating activity. The aa change between adult and neonatal isoforms is at a similar juxta-TM domain position (between I-S3 and I-S4).
 - (2) Ser1773Tyr; normal: ATC ATA TcC TTC CTG, patient R9049 (affected with IGE): ATC ATA TmC TTC CTG :(TCC>TAC). This mutation is in the middle of IV-S6 TM domain; found in 1/70 IGE patients, and 0/150 control subjects tested. This mutation is interesting from a biological point of view for a number of reasons. First, this region of SCN gene (IV-S6) has been found to play a critical role in fast inactivation of the SCN, by mutagenesis experiments in rat SCN (McPhee et al., 1998). This is highly relevant for pathophysiology of epilepsy, since this may increase neuronal hyperexcitability. Moreover, in patients with GEFs, a mutation has been found in the SCN1B subunit, causing impairment of the fast inactivation of the SCN (Wallace et al, 1999). Finally, many of the antiepileptic drugs (e.g. phenytoin, carbamazepine) primarily act by reducing the repetitive firing of neuron, which also involves fast inactivation of the SCN.

EXAMPLE 4**Mutations in SCN2A in IGE patients**

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 4. Following PCR, SSCP analysis was performed and mutations in SCN2A were identified as follows (Figure 5):

- (1) Lys908Arg: normal: TAC AAA GAA for patient numbers always preceded by R; R9782 (Patient with IGE): TAC AGA GAA. The mutation is thus a conservative aa change, located in an extracellular domain between TM domains IIS5 and IIS6; in 1/70 IGE patients; 0/96 normal controls. The mutation involves an important component of the SCN gene, since the S5 and S6 segments are thought to form the wall of the transmembrane pore which allows the sodium to enter the cell. This may have an influence on the gating control of the pore.
- (2) Leu768Val, in individuals R8197, R9062 and R9822 (all IGE patients) (found in 3/70 IGE patients and 0/65 control subjects). The mutation is in the IV-S6 component of the sodium channel, which is important in the inactivation of the channel (see above for more detail).

EXAMPLE 5**Mutations in SCN3A in IGE patients**

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 6. Following PCR, SSCP analysis was performed and mutations in SCN3A were identified as follows (Figure 7):

- (1) Asn43DEL: allele 1: CAA GAT AAT GAT GAT GAG ; allele 2: CAA GAT --- GAT GAT GAG ; in open reading frame deletes 1 aa: DNDDEN->QDDDEN, in the cytoplasmic N-terminal segment; in IGE patients, the frequency of allele 1 = 131/146 (0.90); allele 2= 15/146 (0.10); for IGE patients: homozygotes (22): R3958, R9632; heterozygotes (12): R9049,

R9152, R9649, R9710, R9896, R10069, R10191, R10213, R9993, R10009, R10256 . Of note, 2 patients are homozygous for the rare allele and all patients have IGE. In controls: allele 1 = 145/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes were found.

- 5 (2) normal: `tggtgtaaggtag`, R10670 (IGE patient): `tggtataaggtag`, in conserved intron between 5N & 5A exons, significance uncertain.
- (3) normal: `ccccttatatctccaac`, R10250 (IGE patient): `ccccttatayctccaac`; in conserved intron between 5N & 5A exons, significance uncertain.
- (4) Val1035Ile: normal: `AAA TAC GTA ATC GAT`, R9269 (IGE patient):
 10 `AAA TAC RTA ATC GAT` ; (GTA>ATA = Val>Ile). The mutation is thus a conservative aa change which destroys a *Sna*BI site (this could thus be used as a polymorphism identifiable by restriction enzyme digestion). In SCN1A, this Val is a Ile, therefore probably not a causative mutation. In cytoplasmic domain bw II-S6 & III-S1 TMs; found in 1/70 IGE alleles; and
 15 0/70 controls.

EXAMPLE 6

SCN1A is involved in idiopathic generalized epilepsy

- 20 The assumption that SCN1A gene is involved in idiopathic generalised epilepsy in humans is based on many sets of evidence. First, a mutation has been found in a large Australian family with autosomal dominant epilepsy. The phenotype is idiopathic generalised epilepsy that is associated with febrile seizures (GEFS syndrome). The gene for this family has been previously mapped to the
 25 long arm of chromosome 2. The maximum lod score is 6.83 for marker D2S111. The candidate region is very large, spanning 21cM between markers D2S156 and D2S311. However, within this interval, there is a

cluster of sodium channel genes, including SCN1A which was hypothesized to be a candidate gene for the disease.

Screening by SSCP of a small panel of three (3) affected patients from the family, and 3 normal controls was carried-out at first. All the exons of the SCN1A gene have been amplified by PCR, and a SSCP variant in exon 4 was found for all of the affected individuals, and none of the controls. By sequencing an affected patient and a control, an A-T substitution at nucleotide 565 was found. This variation destroys a BamHI restriction site, this enzyme was thus used as a diagnostic test to screen all the affected patients from the family, as well as more control cases. All affected patients from the family have A565T substitution, and none of the unaffected patients in the same kindred. An A565T substitution was not found in more than 400 control chromosomes.

The A565T substitution correspond to a non-conservative amino acid change (D188V). This amino acid is conserved in all sodium channels thus far identified, in all species. The only exception is SCN2A identified in rat by Numa et al, where the aspartic acid is replaced by asparagine. However, it is likely that this represents an error during replication of cDNA, since other investigators have cloned the same gene in rat and found that the aspartic acid is conserved at position 188. Moreover, the same group has shown that D188N has a functional effect on channel activation in oocytes (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Of note, this A565T substitution has not been found in 150 epileptic patients and in 200 control patients. Thus, this substitution has yet to be identified after 700 chromosomes assessments.

In view of proving that D188V in SCN1A, identified in the large Australian family studied, is a pathogenic mutation, the oligonucleotide mismatch mutagenesis technique was used to introduce the mutation in rat SCN1A clone. RNA was isolated from mutant and wild-

type clones, and injected into oocytes in view of recording sodium currents by the patch-clamp technique. The amplitude of the currents was dramatically reduced for the mutant. Also, a small shift in the inactivation curve was observed for the mutant, as compared to the wild-type. Taken
 5 together, these preliminary results confirm a functional effect of D188V mutation on SCN1A gene. (more detail below).

The results presented herein are corroborated by studies from other investigators. For example, several other groups have also found linkage to the same locus on chromosome 2 for families with
 10 GEFS or very similar syndromes. Mutations in SCN1A (Thr875Met mutation; Arg1648His) have been found to be the cause of the epileptic syndrome in at least two (2) of these families (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Also, GEFS syndrome has been shown to be caused by mutation in SCN1B gene. It is demonstrated that the beta
 15 subunits interact with alpha subunits of voltage-gated sodium channels to alter kinetics of sodium currents in cells. These data suggest a common mechanism for generating abnormal neuronal discharges in the brain of patients with idiopathic generalised epilepsy.

Finally, in the process of screening patients from the
 20 large kindred with GEFS described above, a large cohort of patients with idiopathic generalised epilepsy was also screened by SSCP. Two (2) SSCP variants, that were subsequently sequenced were thereby identified. The variation observed are shown in Table 3:

Table 3

exon	DNA variation	IGE alleles	Control alleles
1Ax17	Glu1238Asp; conservative AA change in extracellular domain between III-S1 and III-S2	3/254	0/284
1Ax24.2	Ser1773Tyr; middle of IV-S6 TM domain	1/252	0/334

- Previous functional studies have shown that amino acid substitution in the IV-S6 transmembrane domain of SCN2A significantly affects the rate of inactivation of the channel. It is thus likely that Ser1773Tyr will have an effect on the SCN1A gene function. Such functional studies are currently underway.

EXAMPLE 7

10 Further validation of the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE and epilepsy in general

- A number of methods could be used to further validate the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE. For example, additional patients could be screened for mutations in SCN1A, SCN2A, or SCN3A. Furthermore, additional normal patients could be screened in order to validate that the mutations identified significantly correlate with disease, as opposed to reflecting a polymorphism which is not linked to IGE. Polymorphisms which are not directly linked to IGE, if in linkage disequilibrium with a functional mutation

linked to IGE, could still be useful in diagnosis and/or prognosis assays. In addition, functional studies can be carried. Numerous methods are amenable to the skilled artisan. One particularly preferred functional assay involves the use of *Xenopus* oocytes and recombinant constructs

5 harboring normal or mutant sequence of SCN1A, SCN2A, or SCN3A. *Xenopus* oocytes have been used in functional assays to dissect the structure-function relationship of the cyclic AMP-modulated potassium channel using recombinant KCNQ2 and KCNQ3 (Schroeder et al., 1998). As well, it has been used to dissect the structure-function relationship of

10 the beta subunit of the sodium channel (SCN1B gene; Wallace et al. 1998).

One such example of functional studies was investigated by assessing the effects of mutation D188V in the SCN1A gene on sodium channel function by introducing the mutation into a cDNA

15 encoding the rat ortholog SCN1A gene. This rat gene shares > 95% identity with the human SCN1A gene. The expression of wild type and mutant channels in *Xenopus* oocytes, and the examination of their properties using voltage-clamp electrophysiological recording is amenable to this *Xenopus* system. Wild type sodium channels are closed at

20 hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid

25 activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds. Among the channel properties that are likely to be altered by mutations linked to epilepsy are: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels; 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential, and 3) the time course of inactivation. Preliminary results indicate that D188V mutant channels are identical to wild type channels with respect to the voltage-dependence of activation and to inactivation time course. However, steady state inactivation for the mutant channels is shifted to membrane potentials that are slightly more positive than observed in wild type channels. This positive shift should increase the fraction of channels available to open at rest. This could increase neuronal excitability and contribute to epileptogenesis. Thus, a functional consequence of a naturally occurring mutation in a sodium channel gene has been tentatively identified. Thus, the functional consequence of the D188M mutant could at least in part explain its role in epilepsy. Such a functional consequence is expected to be observed with other mutations identified above in SCNA1, SCNA2 and SCNA3.

It is recognized by the inventors that certain therapeutic agents have been identified for cardiac, muscular, chronic pain, acute pain and other disorders, and analgesics and anesthetics that are modulators of sodium channels. Use of these sodium channel modulators for treating epilepsy and related neurological disorders also falls within the scope of this invention. In one embodiment of this invention, sodium channel blockers are modified to achieve improved transport across the blood brain barrier in order to have direct effect on neuronal SCNA proteins and genes. Descriptions of such compounds are found at Hunter, JC et al. *Current Opinion in CPNS Invest. Drugs*. 1999 1(1):72-81; Muir KW et al. 2000. *Cerebrovasc. Disc.* 10(6):431-436; Winterer, G. 2000 *Pharmacopsychiatry* 33(5):182-8; Clare et al. 2000. *Drug. Discov. Today* 5(11):506-520; Taylor CP et al. 2000. *Adv. Pharmacol.* 39:47-98, and Pugsley MK et al. 1998 *Eur. J. Pharmacol.* 342(1)93-104.

It is also recognized by the inventors that compounds which modulate (i.e. either upregulate or downregulate) transcription and translation of SCNA genes are useful for treating epilepsy or related neurological disorders. According to this invention, test compounds which modulate the activity of promoter elements and regulatory elements of sodium channel genes are useful for treating these disorders.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

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WHAT IS CLAIMED IS:

1. A method of determining an individual's predisposition to epilepsy and/or development of epilepsy, as well as predicting this individual's response to medication, said method comprising the step of determining the genotype of at least one gene selected from SCN1A, SCN2A and SCN3A of the individual, or of a DNA variant, equivalent, or mutation which shows a linkage disequilibrium therewith, thereby determining an individual's predisposition to epilepsy and/or development of epilepsy.
2. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises restriction endonuclease digestion.
3. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises hybridizing with allele specific oligonucleotides.
4. The method of claim 1, which further comprises a step, prior to determining the SCN1A, SCN2A or SCN3A genotype, of amplifying a segment of the the SCN1A, SCN2A or SCN3A using polymerase chain reaction.
5. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises a sequencing of SCN1A, SCN2A or SCN3A , or parts thereof.
6. The method of claim 1, wherein the SCN1A, SCN2A or SCN3A genotype is determined using a polymorphic variant

site in linkage disequilibrium with at least one allelic variant or mutant identified in accordance with the present invention.

7. An assay for screening a test agent and selecting an agent which modulates inactivation of a sodium channel involved in epilepsy comprising:

- a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and
- b) assaying a function of said sodium channel;
- wherein an agent can be selected when an observable difference is observed between the inactivation of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

8. An assay for screening a test agent and selecting an agent which modulates the activity of a sodium channel involved in epilepsy comprising:

- a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and
- b) assaying the activity of said sodium channel;
- wherein an agent can be selected when an observable difference is observed between the activity of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

9. A method of using specific alleles of the SCN1A, SCN2A or SCN3A genes, or a variant, equivalent, or mutation thereof which shows linkage disequilibrium therewith, to set-up a screening assay

for agents destined to modulate sodium channel function for the purpose of identifying agents having an application in epilepsy therapy.

10. A method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising:

- a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;
- b) contacting said screening assay with a test compound; and
- c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

15

11. The method of claim 10, wherein the test compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide further analogs of said test compound also having said therapeutic effect.

20

12. A compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising,

- a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;
- b) contacting said screening assay with a test compound; and
- c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

25

ABSTRACT OF THE DISCLOSURE

The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognose or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention also provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders .

Ch 2q23-q31

Centromere

1cM	D2S142
	D2S284
4cM	
4cM	D2S156/
	D2S354
	D2S111
5cM	
	D2S294
2cM	
	D2S335
6cM	
2cM	D2S324
2cM	D2S384
	D2S152
8cM	

IGE locus

29 cM

Telomere

D2S311

FIGURE 1

1Ax00.1

NaC-340 TGTGTTCTGCCCCAGTGAGACT

NaC-341 CTCCTGCTCTGCCCAAACCTGAAT

257 bp 53.4C

1Ax00.2

NaC-342 GGCGATGTAATGTAAGGTGCTGTC

NaC-343 GTGCCTTCAGTTGCAATTGTTCAG

259bp 54.5C

1Ax01.1

NaC-268, TTAGGAATTTTCATATGCAGAATAA,

NaC-269 TGGGCCATTTTTTCGTCGTC

201 bp 50.9C

1Ax01.2

NaC-270 GAAAGACGCATTGCAGAAGAAAAGG,

NaC-271 CTATTGGCATGTGTTGGTGCTACA

277bp 54.4C

1Ax02

NaC-45 GTGCTGGTTTCTCATTTAACTTTAC,

NaC-46 TTCCCAACTTAATTTGATATTTAGC,

319 bp 49.9C

1Ax03

NaC-87, GCAGTTTGGGCTTTTCAATGTTAG,

NaC-88, GACACAGTTTCARAATCCCRAATG,

234 bp 48.9C

1Ax04

NaC-63, TTAGGGCTACGTTTCAATTTGTATG,

NaC-64, AGCACTGATGGAAAACCAAACCTAT,

338 bp 50.8C

1Ax05

NaC-164 AGCCCATGCAGTAATATAAATCCT

NaC-165 TCCAGGCTGATAAGCTATGTCTAA,

488 bp 52.8C

1Ax06

NaC-276, CTGTGGCCTGCCTGAGCGTATT,
NaC-277 CCAATTCTACTTTTAAAGGAAATG,
248bp 50.3C

1Ax07

NaC-272, AAATACTTGTGCCTTTGAA,
NaC-273, GTACATACAATATACACAGATGC
240 bp 46.7C

1Ax08

NaC-89, AGGCAGCAGAACGACTTGTAATA,
NaC-90, ATCCGGTTTTAATTCATAACTCA,
267 bp 51.9C

1Ax09.2

NaC-217 GTTGAGCACCTTAGTGAATAATA,
NaC-218 TCACACGCTCTAGACTACTTCTCT
337bp 52.7C

1Ax10a NaC-29, TGCAAATACTTCAGCCCTTTCAA,
NaC-30, TTCCCCACCAGACTGCTCTTTC,
239bp, 55.1C

1Ax10a

NaC-31, GCAGCAGGCAGGCTCTCA,
NaC-32, TCTCCCATGTTTTAATTTCAACC,
293bp, 54.5C

1Ax10b

NaC-67, ATAATCTTGCAAAATGAAATCACA,
NaC-68, ATCCGGGATGACCTACTGG
307 bp 53.7C

1Ax10b

NaC-65, GATAACGAGAGCCGTAGAGATTCC,
NaC-66, AGCCAGCCATGCCTGAACTA
282bp 56.4C

FIGURE 2 (cont'd)

(2/6)

1Ax10c

NaC-39, TGTTTGCTTGTCATATTGCTCAA,

NaC-40, TGCACTATTCCTCAACTCACAAA,

286bp, 50.7C

1Ax11.1

NaC-69 AAGGGTGTCTCTGTAACAAAAATG,

NaC-70, GTGATGGCCAGGTCAACAAA

269bp 50.8C

1Ax11.2

NaC-71 CTGGGACTGTTCTCCATATTGGTT,

NaC-72, TTTGCAGGGGCCAGGAAG

294 bp 53.3°C

1Ax12

NaC-41 CATTGTGGGAAAATAGCATAAGC,

NaC-42, GCAAGAACCCTGAATGTTAGAAA,

334bp, 51.2C

1Ax13.1

NaC-92 TAATGCTTTTAAGAATCATACAAA,

NaC-93, CCAGCGTGGGAGTTGACAATC,

256bp, 51.1C

1Ax13.2

NaC-75 CGGCATGCAGCTCTTTGGTA,

NaC-91, ATGTGCCATGCTGGTGTATTTC,

277 bp 55.6C

1Ax14.1

NaC-79 CACCCATCTTCTAATCACTATGC,

NaC-80, CAGCAATTTGGAGATTATTCATT,

254 bp 50.4C

1Ax14.2

NaC-81 GCAGCCACTGATGATGATAA,

NaC-82, CTGCCAGTTCCTATACCACTT,

269 bp 49.4C

FIGURE 2 (cont'd)

(3/6)

1Ax14.3

NaC-83 TACAGCAGAAATTGGGAAAGAT,
NaC-84, GTATTCATACCTACCCACACCTAT,
269 bp 50.2C

1Ax15

NaC-202 TTCTTGGCAGGCAACTTATTACC,
NaC-203 TAAGCTGCACTCCAAATGAAAGAT
233bp 53.1C

1Ax16.1

NaC-187, GGCTGAATGTTTCCACAACCT,
NaC-168 GTTCAACTATTCGGAACACG
277 bp, 51.4C

1Ax16.2

NaC-188, AGGCAGAGGAAAACAATGG,
NaC-189, ACAAGGTGGGATAATTAAAAATG
234 bp, 50.3C

1Ax17

NaC-143, GTTTCTCTGCCCTCCTATTCC,
NaC-144, AAGCTACCTTGAACAGAGACA,
330 bp, 48.8C

1Ax18

NaC-139, AATGATGATTCTGTTTATTA,
NaC-140, AATTTGCCATTCCTTTTG,
272 bp, 46.1C

1Ax19.1

NaC-219 TTGACATCGAAGACGTGAATAATC,
NaC-220 CCATCTGGGCTCATAAACTTGTA
285bp 49.3C

1Ax20

NaC-338 CCCTTTGAAAATTATATCAGTAA,
NaC-339 ATTTGGTCGTTTATGCTTTATTC
230 bp 47.6C

FIGURE 2 (cont'd)
(4/6)

1Ax21
NaC-252, TCCAGCACTAAAATGTATGGTAAT,
NaC-253, ATTTGGCAGAGAAAACACTCC
261 bp 49.8C

1Ax22
NaC-254, TTTTAGCCATCCATTTTCTATTTT,
NaC-255, TATTTTCCCCCATATCATTGA
223 bp 49.1C

1Ax23.1
NaC-256 TTTGCAAGAACTAGAAAGTC,
NaC-257 TTGATGCGTGACAAAATGG
250bp 48.3C

1Ax23.2
NaC-258 GACCAGAGTGAATATGTGACTACC,
NaC-259 CTGGGATGATCTTGAATCTAATC
246bp 49.5C

1Ax24.1
NaC-221 GCAACTCAGTTCATGGAATTTGAA,
NaC-222 CTTGTTTTTCGTTTTAAAGTAGTA
289bp 56.1C

1Ax24.2
NaC-213 CAAAGATCACCCCTGGAAGCTCAGTT,
NaC-223 TTCAAGCGCAGCTGCAAAGTGAAT
277bp 55.8C

1Ax24.3
NaC-260 ACATCGGCCTCCTACTCTTCCTA,
NaC-261 ACAGATGGGTTCACACAGTCC
268 bp 55.3C

1Ax24.4
NaC-262 TAACGCATGATTTCTTCACTGGTT,
NaC-263 ATCCCAAAGATGGCGTAGATGA
262 bp 54.9C

FIGURE 2 (cont'd)

(5/6)

1Ax24.5
NaC-308, TGAGAAATAGGCTAAGGACCTCTA,
NaC-309 CCTAGGGGCTGGATTCC
244 bp 53.2C

1Ax24.6
NaC-310, AAGGGGTGCAAACCTGTGATTTT,
NaC-311 AGGGCCATGTGGTTGCCATAC
252 bp 53.4C

1Ax24.7
NaC-312 CTTCCGGTTTATGTTTTTCATTTCT,
NaC-313 TCTTTATTAGTTTTGCACATTTTA
278bp 48.4C

1Ax24.8
NaC-364 CAATCCTTCCAAGGTCTCCTATC,
NaC-365 TTTCATCTTTGCCTTCTTGCTCAT
326bp 52.4C

1Ax24.9
NaC-366 CATGTCCACTGCAGCTTGTCCA,
NaC-367 TCCCCTTTACACAGAGTCACAGTT
292bp 53.1C

FIGURE 2 (cont'd)

(6/6)

a. Glu1238Asp:
normal: GCA TTT GAA GAT ATA;
patient R10191 with IGE: GCA TTT GAC GAT ATA.

b. Ser1773Tyr:
normal: ATC ATA TcC TTC CTG;
patient R9049 with IGE: ATC ATA TmC TTC CTG; TCC>TAC

FIGURE 3

2Ax00.1 NaC-235 ATGGGTTGAATGACTTTCTGACAT, NaC-236
AGGCATTTCTGTACAGGGACTAC
266bp 52.7C

2Ax00.2 NaC-237 ACAGGAAATGCCTCTTCTTACTTC, NaC-238
TTTCCCCAAGGATTCTACTACTGT
277bp 50.6C

2Ax01 NaC-100, AGTGCATGTAAGTACACAATCAC, NaC-101,
CTTGCGTTCCTGTTTGGGTCTCT
241 bp 53.7C

2Ax01 NaC-11 TCCGCTTCTTTACCAGGGAATC, NaC-102,
AGGCAGTGAAGGCAACTTGACTAA, 259
bp 55.1C

2Ax02 NaC-96, CAGGGCAATATTTATAAATAATGG, NaC-97,
TTTGGAATAATGTGTAGCTCAATAA,
289 bp 48.7C

2Ax03 NaC-43, AAGGCATGGTAGTGCATAAAAG, NaC-44,
ATGAAACATAAAGGGAGGTCAA, 201
bp, 49.3°C

2Ax04 NaC-47, AATGTGAGCTTGGCTATTGTCTCT, NaC-48,
ATAGGCTCCCACCAGTGATTTAC,
213 bp, 50.9°C

2Ax05 NaC-49, AGGCCCCTTATATCTCCAAGT, NaC-50,
CAACAAGGCTTCTGCACAAAAG, 241
bp, 53.9°C

2Ax05.2 NaC-110, CTTGGTGGCTTGCCTTGAC, NaC-111, TCATGAGTGTCGCCATCAGC,
223
bp, 51.1C

2Ax05.3 NaC-112, GGAAAGCTGATGGCGACACT, NaC-113,
CTGAGACATTGCCCAGGTCC, 329
bp 53.0C

FIGURE 4
(1/6)

2Ax05.4 NaC-114, TTTTACCCGTTGCTTTCTTTA, NaC-115,
TATCCCTTGCTCTTTCATTTATCT
224bp 50.9C

2Ax06.1 NaC-169, GCCGGTAAAATAGCTGTTGAGTAG, NaC-170,
GCCATTGCAAACATTTATTTTCGTA 206bp 53.3C

2Ax06.2 NaC-171, GCGTGTTTGCGCTAATAG, NaC-172,
CTAAGTCACTTGATTACATCTAA
295bp 48.0C

2Ax07 NaC-196, ACAGGGTGGCTGAAGTGTTTTA, NaC-197,
GTGGGAGGTGGCAGGTTATT, 199
bp, 52.6C

2Ax08 NaC-118, CAATTAGCAGACTTGCCGTTATT, NaC-119,
TCTCTTGAGTTCGGTGTTTATGA
252bp 52.9C

2Ax09 NaC-120, ACCGAACTCAAGAGAATTGCTGTA, NaC-121,
AAAGGACCGTATGCTTGTTCACTA
334bp 52.9C

2Ax10a.1 NaC-161 TATGAATGCGCATTTTACTCTTTG, NaC-156
TGGAGCTCAACTTAGATGCTACTG
286 bp 52.1C

2Ax10a.2 NaC-13 GGTGCTGGTGGGATAGGAGTTTTT, NaC-162
TCCATTAAATTCTGGCATATTCTT,
316 bp 50.9C

2Ax10b.1 NaC-145 TCAGAGGGGTGCTTTCTTCCACAT, NaC-14
CTTCGGCTGTCATTGTCCTCAAAG,
298bp 55.6C

2Ax10b.2 NaC-146, GCAAAGGACATTGGCTCTGAGAAT, NaC-
147, CTGCCTGCACCAGTCACAACTCT
324bp 59.4C

FIGURE 4 (cont'd)
(2/6)

2Ax10c NaC-190, TGGGCTTTGCTGCTTTCAA, NaC-191,
AGTAACTGTGACGCAGGACTTTTA, 218
bp 51.5C

2Ax11.1 NaC-148, CCCTGTTCTCCAGCAGATTA, NaC-70
GTGATGGCCAGGTCAACAAA, 283
bp, 51.5C

2Ax11.2 NaC-149,TTTGATTTGGGACTGTTGTAAAC, NaC-
150,AAGGCAATTATAAACTCTTTCAAG
233bp 52.0C
2Ax12 NaC-159, TGGGAGTTAAATTAAGTTGCTCAA, NaC-160,
ACATTTTATGAACACTCCCAGTTA
285bp 50.4C

2Ax13.1 NaC-239 ATTAACACTGTTCTTGCTTTTAT, NaC-240
GTGCCAGCGTGGGAGTTC 239 bp
51.1C

2Ax13.2 NaC-241 GTGGGGGCTCTAGGAAACCT, NaC-242
TTTAATGAAAATGAGGAAAATGTT 324
bp 53.7C

2Ax14.1 NaC-134, GACCAAGCATTTTTATTTTCATTC, NaC-135,
AGTGGCAGCAAGATTGTCA 234
bp, 49.6C

2Ax14.2 NaC-136, GGCCTTGCTTTTGAGTTCC, NaC-137,
GGTCTTGCCTATTTCTATGGTG, 257
bp, 51.1C

2Ax14.3 NaC-266, TTAAACCGCTTGAAGATCTAAATA, NaC-267
TATACACCAAATATCTCCTTAT
319bp 48.5C

2Ax15 NaC-314 GGGGCACACCTAATTAATTTTTAT, NaC-315
AAAGAGGATACTCAAGACCACATA
(247bp) 51.5C

FIGURE 4 (cont'd)

(2/6)

2Ax16 NaC-344 CCCACCAACACAAATATACCTAAT, NaC-345
TGAAGGGAAAGGGAAAAGATTT
283bp 52.2C

2Ax17 NaC-346 TCCAGCCTTAGGCACCTGATAA NaC-347
ATAAAGCAGCAAAGTGCAGCATAC 310bp
52.4C

2Ax18 NaC-348 AAGGCTGAACTGTGTAGACATTTT NaC-349
TGACATTTCCATGGTACAAAGTGT
262bp 52.2C

2Ax19.1 NaC-350 TTTGTTGTTGGCTTTTCACTTAT NaC-351
CCACCTGGCAGTTTGATTG 268bp 51.9C

2Ax19.2 NaC-352 TAAGCGTGGTCAACAACTACAGT NaC-353
ATTCTTGCCAGCATTTATTGTC
260bp 50.2C

2Ax20 NaC-354 CAAAACATTGCCCCAAAAG NaC-355
TCAAACATAACAATTTCCCTCTAA 239 bp 48.1C

2Ax21 NaC-306, GATAATTAAAACTCACTGATGTA, NaC-307
GGAGGCTAAAGGAAAGAGTATG
288bp 46.6C

2Ax22 NaC-356 ATTTTATAGCCAGCAAAGAACAC NaC-357
CTAGAAATTCGGGCTGTGAA 230 bp 49.6C

2Ax23.1 NaC-358 CTGCTTTGTGACCTAAGGCAAGTT NaC-359
GTGACCATGTTAAGGCAGATGAGG
290bp 51.4C

2Ax23.2 NaC-360 GGAATGGTCTTTGATTTTGTAACC NaC-361
TCCTTAACTGAATAAAAGCACCTC
290bp 51.6C

2Ax24.1 NaC-207 TGGAACACCCATCAAAGAAGATACT, NaC-208
GTGGGAGTCCTGTTGACACAAAC
278bp 52.8C

FIGURE 4 (cont'd)
(4/6)

2Ax24.2 NaC-209 AGCGATTCATGGCATCAAAC, NaC-210
ACGTGGTGGGAAGGCGTCATA 270 bp,
52.9C

2Ax24.3 NaC-211 GCGACCCAGTTTATAGAGTTTGCC, NaC-212
CTTGTTTGCGTTTCAACGTGGTC
289bp 56.1C

2Ax24.4 NaC-213 CAAAGATCACCCCTGGAAGCTCAGTT, NaC-214
ATCCAGGGCATCTGCAAAATCAGAA
277bp 55.8C

2Ax24.5 NaC-215 TGCCTATGTTAAGAGGGAAGTTGGG, NaC-216
ATGACCGCGATGTACATGTTTCA
279bp 55.3C

2Ax24.6 NaC-278 TCAATTGTTTACAGCCCGTGATG, NaC-279
TTTATACAAAGGCAGACAACAT
302bp 52.0C

2Ax24.7 NaC-280 AGGCGTAATGGCTACTCAGACGA, NaC-281
GTAATCCCTCTCCCCGAACATAAAC
251bp 53.8C

2Ax24.8 NaC-282 TTTGATTCACGGGTGTTTACTCTTA, NaC-283
TTCTATGGAACATTTACAGGCACATT 294bp 52.1C

2Ax24.9 NaC-284 TAATGTGCCTGTAAATGTTCCATAGA, NaC-285
CAGGCTTCTTAGAAAGGACTGATAGG 264bp 50.6C

2Ax24.10 NaC-286 GTCCCAGCAGCATGACTATC, NaC-287
CCCACTGGGTAAAATTACTAAC 249bp
49.4C

2Ax24.11 NaC-288 TAGCCATCTTCTGCTCTTGGT, NaC-289
TGGCTTCCCATATTAGACTTCTG
307bp 51.3C

2Ax24.12 NaC-290 TCTTGCCTATGCTGCTGTATCTTA, NaC-291
AGTCGGGCTTTTCATCATTGAG
207bp 51.8C

FIGURE 4 (cont'd)

(5/6)

2Ax24.13 NaC-292 TTCTTCATGTCATTAAGCAATAGG, NaC-293
TTCAATTTAAAAGTGCTAGGAACA
299bp 49.4C

2Ax24.14 NaC-294 CTTTCAGGTGGATGTCACAGTCACTA NaC-295
ATTCAAGCAATGCCAAGAGTATCA
263bp 51.5C

2Ax24.15 NaC-296 CTTTCAATAGTAATGCCTTATCAT NaC-297
TCCTGCATGCATTTACCAAC
348bp 49.6C

2Ax24.16 NaC-362 CTGTTACATTTTGTA AAACTAAT, NaC-263
ATCCCAAAGATGGCGTAGATGA
309 bp 50.8C

2Ax24.17 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-363
GATCTTTGTCAGGGTCACAGTCT 269
bp 54.0C

FIGURE 4 (cont'd)

(6/6)

a. Lys908Arg:
normal: TAC AAA GAA;
9782 (Patient with IGE): TAC AGA GAA;

b. leu768val, in individuals 8197, 9062 et 9822 (all IGE patients).

FIGURE 5

3Ax00a.1 NaC-390 TGTGTCCGCCAGTAGATGG, NaC-391
TTTTTGACCACAGAGGTTTACAA 233bp
51.4C

3Ax00a.2 NaC-392 GAAGCGGAGGCATAAGCAGA, NaC-393
GGTGCAGATAATGAAATGTTTTGT
253bp 51.3C

3Ax00b NaC-394 CACCCCTATGCCAAATGTCAAAGA NaC-395
CAAAAACAAACTTATACCCAGAAG
293bp 51.6C

3Ax00c NaC-396 CAAATATTGGGCAAACCCTAAT, NaC-397
AAGGTGCCATCACAAAATCAT 225bp
50.7C

3Ax01.1 NaC-51 ATCGCTTGCTTTCCTAACTCTTGT, NaC-52
AAGTCACTATTTGGCTTTGGTTG,
260bp, 53.1C

3Ax01.2 NaC-53 AGAAGCCCCAAAAAGGAACAAGATA, NaC-54
GGCCCAGAAAAGTATATTACAGTT,
231bp, 50.8C

3Ax02 NaC-85, TCCTTAAATAAGCCCATGTCTAAT, NaC-86,
TCTCAAAGAAATTTTACAGATACT,
273bp, 47.3C

3Ax03 NaC-27, AATGGCCATGGTAACCTACTAACA, NaC-28,
CAGGCTATACCCACAAGGAGATT,
212 bp 51.8C

3Ax04 NaC-94, TGTTAATTTTGGCTTGGATGTT, NaC-95,
TCACTCCTTTGCGCTTATCAA, 198 bp
50.8C

3Ax05.1 NaC-247, AGGGCTCTATGTGCCAAACC, NaC-248,
AGGGGCCTACTACCTTACACCAG 213
bp 52.2C

FIGURE 6
(1/5)

3Ax05.2 NaC-249 TGTAATCCCAGGTAAGAAGAAAC, NaC-250
TACCGGGATGAACTGTAATAATAA
304 bp 51.8C

3Ax06.1 NaC-192,TTCTGGCACTCTTCCTCAGGTAAC, NaC-
193,GTCCCATTTGAATCCATTGTGC,
261bp 55.4C

3Ax06.2 NaC-194,GGCCCCCAAGCGATTCTG, NaC-195,
TGTACACCCACAGTCTCAACTATT,
209bp, 50.3C

3Ax07 NaC-204, ACAGCCACCTTTGTAAATAA, NaC-205,
TTTTTCGCAAAGAGTTCTAT
220 bp, 46.6C

3Ax08 NaC-98, AAAGTACCCTACCTCCATTTCTC, NaC-99,
ACTCAGCCTATGCTTTTCATTCA,
247 bp 53.2C

3Ax09 NaC-37 CAGATATTTATTTGGGGACATTAT, NaC-38
AAATCTTTGCKTTTATCACTCAGT, 295
bp, 52.0C

3Ax10a.1 NaC-198 TAGTGCCTGGCTTTGTTTATGAC, NaC-199
CGGATTTGGGAAAGCTGTCTCT
225 bp 54.3C

3Ax10a.2 NaC-200 AGAGCACCTTGAAGGAAACAACAA, NaC-274,
TCCCTCAACTGAAGTACAGATAGT, 253 bp 51.2C

3Ax10b NaC-33, ATAATTGCGTTCTTCCCCTACCC, NaC-34,
AAGCCCTGGCACCATCCTG, 301
bp, 56.2°C

3Ax10c NaC-35, _TTTGCAAAGAAATGCTATGT, NaC-36,
CTGGGTAACAGACTTCAGTAAT, 303
bp, 51.4°C

3Ax11.1 NaC-122, ATGGGATTGTCTTCTCAAGTTTCT, NaC-123,
GATGGCAAGATCAACAAATGGA
294bp 50.3C

FIGURE 6 (cont'd)

(2/5)

3Ax11.2 NaC-124, CTTGATCTGGGACTGCTGTGATG, NaC-125,
AGGATATAATTTTTGGTTCAACA
284bp 51.5C

3Ax12 NaC-61, TTTTCAGTGCTCTTGATAGTAGTG, NaC-62,
GTGCCAATGAGCGACAGG, 254 bp,
50.7°C
3Ax13.1 NaC-73, CCACGTGTGGTTCTATGATACC, NaC-74,
ACCGTGGGAGCGTACAGTCA 298 bp
52.3C

3Ax13.2 NaC-75, CGGCATGCAGCTCTTTGGTA, NaC-76,
TGGCCACGTTCCCTAGCTACTGTC 291
bp 55.9C

3Ax14.1 NaC-55, GAGTTCCCTTTTTAGGCTGTTATT, NaC-56
TCTTATTGCCTTCATGGATTCTA,
285bp,50.5C

3Ax14.2 NaC-57, TGAAAAATAAGATGCGGGAGTG, NaC-58,
GTGAGGCTGGGGTTGTTTATG, 247
bp, 51.7C

3Ax14.3 NaC-59, GAGATGGGAATGGAACCACCA, NaC-60,
TTCGATAATGCATATAAGCACAA, 297
bp, 51.7C

3Ax15 NaC-318 AAGGGGGAAAATCACATCTTT, NaC-319
TTAAATGAGGCATATTCAGTCTCC 235bp
51.8C

3Ax16 NaC-116, GGAAGTGGAGTGGGGAAGG, NaC-117,
ATTCTTGCCAATATGCATTCACT, 271
bp, 51.1C

3Ax17 NaC-157,TTCTTTTGTACTCACTATTATACTAA, NaC-
158,AAACTTGCCTCTTTAAAAACAAT
317bp 46.6C

3Ax18 NaC-374 TACCACACCCTATACCTTCAGTCA, NaC-375
GAGTATGGCACCCCTTTTCTATCTA
275bp 51.4C

FIGURE 6 (cont'd)
(7/5)

3Ax19.1 NaC-386 GCTATGTTCCCCTCGCTGTCT, NaC-387
TGCTTGCCAAGAGCCTGAC
231bp 53.6C

3Ax19.2 NaC-388 GCTGGCAAGTTCTACCACTGTG, NaC-389
CAAACGAAGAACATCAGGGAAATA
247bp 53.0C

3Ax20 NaC-376 TTCACAATATTGTACAAAAGTTA, NaC-377
ATTACCACCAATATTCACCATAAG
230 bp 46.4C

3Ax21 NaC-378 TCAGGGTAAGGCAAAAGTAGCAC, NaC-379
GAACCCGAGAATGAAGAAAGGTAA 294
bp 50.2C

3Ax22 NaC-380 TTTGTGAAAGTACTATTGGAACAC, NaC-381
ACGCATGGCTTTGGAACAT 204bp 49.6C

3Ax23.1 NaC-382 CCCGTATGTGGAAGGGCTTTAT, NaC-383
CTAGGTTGATCCGGGACAAAATA
246bp 52.9C

3Ax23.2 NaC-384 AACGGATGACCAGGGCAAATAC, NaC-385
CTAGAAGGTCCTGGGGCAACTG
234bp 54.8C

3Ax24.1 NaC-317 AAGCCATCATGTAAAGTGAAAAG, NaC-320
ATCCCAAAGATGGCATAGATA 274
bp, 52.5C

3Ax24.2 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-326 TGAGCTGCCAGGGTGAATTG
282 bp 54.9C

3Ax24.3 NaC-327 TTGCTAGCACCTATTCTTAATAGTGC NaC-328
CCAGGGCAGCTGCAAAATCAGAG
318bp 54.2C

3Ax24.4 NaC-329 CCCGATGCGACCCAGTTTA, NaC-330 TGGAGGGGTTTGATGCCATA
250 bp, 55.2C

FIGURE 6 (cont'd)

(4/5)

3Ax24.5 NaC-331 GATGGATGCCCTTCGAATACAGA, NaC-332
TTCCCATTAGTTTGTCAATAATC
258 bp 50.6C

3Ax24.6 NaC-321 AAGGGGAGGATTGACTTACCTAT, NaC-333
TTGGCATGGACCTCCTCTTGA 302
bp 51.5C

FIGURE 6 (cont'd)

(5/5)

a. Asn43DEL:

9706 (allele 1; IGE patient): CAA GAT AAT GAT GAT GAG ;

9632 (allele 2; patient has IGE): CAA GAT --- GAT GAT GAG ;

allele 1 = 131/146 (0.90);

allele 2 = 15/146 (0.10);

for IGE patients: homozygotes (22): 3958, 9632; heterozygotes (12): 9049, 9152, 9649, 9710, 9896, 10069, 10191, 10213, 9993, 10009, 10256 (note that 2 patients are homozygous for the rare allele; all patients have IGE); in controls: allele 1 = 45/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes found.

b. normal: tggtgtaaggtag,

10670 (IGE patient): tggtataaggtag

c. normal: ccccttatatctccaac,

10250 (IGE patient): ccccttatayctccaac;

d. Val1035Ile:

normal: AAA TAC GTA ATC GAT,

9269 (IGE patient): AAA TAC RTA ATC GAT; GTA>ATA = Val>Ile.

FIGURE 7

tactgcagaggtctctgggtcatgtgtgtatgtgtgcgtttgtgtgtgtttgtgtgtctgtgtgttctgccccagtgagactgcagcccttgtaaata
ctttgacaccttttgaagaagggaatctgaacaattgcaactgaaggcacattgtatcatctcgtctttgggtgatgctgttcctcactgcagatg
gataattttccttttaacaggaatttcatatgcagaataaatggtaattaaaatgtgcaggatgacaagATGGAGCAAACAGTGC
TTGTACCACCAGGACCTGACAGCTTCAACTTCTTCACCAGAGAATCTCTTGCGGCTA
TTGAAAGACGCATTGCAGAAGAAAAGGCCAAAGAATCCCAAACCAGACAAAAAAGA
TGACGACGAAAATGGCCCCAAAGCCAAATAGTGACTTGGAAGCTGGAAAGAACCTTC
CATTTATTTATGGAGACATTCTCCAGAGATGGTGTGACAGAGCCCCTGGAGGACCTGG
ACCCCTACTATATCAATAAGAAAACCTTTTATAGTATTGAATAAAaggGAAGGCCA
TCTTCCGGTTCAGTGCCACCTCTGCCCTGTACATTTTAACTCCCTTCAATCCTCTTAG
GAAAATAGCTATTAAGATTTTGGTACATTCATTATTCAGCATGCTAATTATGTGCACT
ATTTTGACAACTGTGTGTTTATGACAATGAGTAACCCTCCTGATTGGACAAAGAAT
GTAGAATACACCTTCACAGGAATATATACTTTTGAATCACTTATAAAAATTATTGCA
AGGGGATTCTGTTTAGAAGATTTTACTTTCCTTCGGGATCCATGGAAGTGGCTCGATT
TCACTGTCATTACATTTGCGTACGTCACAGAGTTTGTGGACCTGGGCAATGTCTCGG
CATTGAGAACATTCAGAGTTCTCCGAGCATTGAAGACGATTTTCAGTCATTCCAGG
CCTGAAAACCATTGTGGGAGCCCTGATCCAGTCTGTGAAGAAGCTCTCAGATGTAAT
GATCCTGACTGTGTTCTGTCTGAGCGTATTTGCTCTAATTGGGCTGCAGCTGTTTCATG
GGCAACCTGAGGAATAAATGTATACAATGGCCTCCCACCAATGCTTCCTTGGAGGA
ACATAGTATAGAAAAGAATATAACTGTGAATTATAATGGTACACTTATAAATGAAA
CTGTCTTTGAGTTTGACTGGAAGTCATATATTCAAGATTCAAGATATCATTATTTCT
GGAGGGTTTTTTAGATGCACTACTATGTGGAAATAGCTCTGATGCAGGCCAATGTCC
AGAGGGATATATGTGTGTGAAAGCTGGTAGAAATCCCAATTATGGCTACACAAGCTT
TGATACCTTCAGTTGGGCTTTTTTGTCTTGTTCGACTAATGACTCAGGACTTCTGG
GAAAATCTTTATCAACTGACATTACGTGCTGCTGGGAAAACGTACATGATATTTTTT
GTATTGGTCATTTTCTTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTGTGGTGG
CCATGGCCTACGAGGAACAGAATCAGGCCACCTTGGAAGAAGCAGAACAGAAAGA
GGCCGAATTTTCAGCAGATGATTGAACAGCTTAAAAAGCAACAGGAGGCAGCTCAGC
AGGCAGCAACGGCAACTGCCTCAGAACATTCCAGAGAGCCCAGTGCAGCAGGCAGG
CTCTCAGACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAAGAGTGCTAAGGAAAGA
AGAAATCGGAGGAAGAAAAGAAAACAGAAAGAGCAGTCTGGTGGGGAAGAGAAAG
ATGAGGATGAATTCCAAAAATCTGAATCTGAGGACAGCATCAGGAGGAAAGGTTTT
CGCTTCTCCATTGAAGGGAACCGATTGACATATGAAAAGAGGTACTCCTCCCC

ACACCAGTCTTTGTTGAGCATCCGTGGCTCCCTATTTTCACCAAGGCGAAATAGCAG
AACAAGCCTTTTCAGCTTTAGAGGGGCGAGCAAAGGATGTGGGATCTGAGAACGACT
TCGCAGATGATGAGCACAGCACCTTTGAGGATAACGAGAGCCGTAGAGATTCTTTG
TTTGTGCCCCGACGACACGGAGAGAGACGCAACAGCAACCTGAGTCAGACCAGTAG
GTCATCCCGGATGCTGGCAGTGTTTCCAGCGAATGGGAAGATGCACAGCACTGTGG
ATTGCAATGGTGTGGTTTCTTGGTTGGTGGACCTTCAGTTCCTACATCGCCTGTTGG
ACAGCTTCTGCCAGAGGTGATAATAGATAAGCCAGCTACTGATGACAATGGAACAA
CCACTGAAACTGAAATGAGAAAGAGAAGGTCAAGTTCTTTCCACGTTTCCATGGACT
TTCTAGAAGATCCTTCCCAAAGGCAACGAGCAATGAGTATAGCCAGCATTCTAACA
AATACAGTAGAAGAACTTGAAGAATCCAGGCAGAAATGCCACCCTGTTGGTATAA
ATTTTCCAACATATTCTTAATCTGGGACTGTTCTCCATATTGGTTAAAAGTGAAACAT
GTTGTCAACCTGGTTGTGATGGACCCATTTGTTGACCTGGCCATCACCATCTGTATTG
TCTTAAATACTCTTTTCATGGCCATGGAGCACTATCCAATGACGGACCATTTCATA
ATGTGCTTACAGTAGGAACTTGGTTTTCTACTGGGATCTTTACAGCAGAAATGTTTCT
GAAAATTATTGCCATGGATCCTTACTATTATTTCCAAGAAGGCTGGAATATCTTTGA
CGTTTTTATTGTGACGCTTAGCCTGGTAGAACTTGGACTCGCCAATGTGGAAGGATT
ATCTGTTCTCCGTTTCATTTTCGATTGCTGCGAGTTTTCAAGTTGGCAAAATCTTGGCCA
ACGTTAAATATGCTAATAAAGATCATCGGCAATTCGCTGGGGGCTCTGGGAAATTTA
ACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGGCATGCAGCTCTTTG
GTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACTCCCACGCT
GGCACATGAATGACTTCTTCCACTCCTTCTGATTGTGTTCCGCGTGCTGTGTGGGGA
GTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTTAC
TGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCTCTGAATCTCTTTCTGGCC
TTGCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGATAATGAA
ATGAATAATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAA
AAGAAAAATATATGAATTTATTCAACAGTCTTTCATTAGGAAACAAAAGATTTTGA
TGAAATTAAACCACTTGATGATCTAAACAACAAGAAAGACAGTTGTATGTCCAATCA
TACAGCAGAAATTGGGAAAGATCTTGACTATCTTAAAGATGTAAATGGAACACAA
GTGGTATAGGAACTGGCAGCAGTGTTGAAAAATACATTATTGATGAAAGTGATTAC
ATGTCATTCATAAACAACCCAGTCTTACTGTGACTGTACCAATTGCTGTAGGAGAA
TCTGACTTTGAAAATTTAAACACGGAAGACTTTAGTAGTGAATCGGATCTGGAAGAA
AGCAAAGAGAACTGAATGAAAGCAGTAGCTCATCAGAAGGTAGCACTGTGGACAT
CGGCGCACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAGAACTCTTGAACCAG
AAGCTTGTTTCACTGAAGGCTGTGTACAAAGATTCAAGTGTTGTCAAATCAATGTGG
AAGAAGGCAGAGGAAAACAATGGTGGAACCTGAGAAGGACGTGTTTCCGAATAGTT
GAACATAACTGGTTTGAGACCTTCATTGTTTTTCATGATTCTCCTTAGTAGTGGTGCTC
TGGCATTGGAAGATATATATATTGATCAGCGAAAGACGATTAAGACGATGTTGGAAT
ATGCTGACAAGGTTTTCACTTACATTTTCATTCTGGAAATGCTTCTAAAATGGGTGGC
ATATGGCTATCAAACATATTTACCAATGCCTGGTGTTGGCTGGACTTCTTAATTGTT
GATGTTTCATTGGTCAGTTTAAACAGCAAATGCCTTGGGTTACTCAGAACTTGGAGCC
ATCAAATCTCTCAGGACACTAAGAGCTCTGAGACCTCTAAGAGCCTTATCTCGATTT
GAAGGGATGAGGGTGGTTGTGAATGCCCTTTTAGGAGCAATTCCATCCATCATGAAT
GTGCTTCTGGTTTGTCTTATATTCTGGCTAATTTTCAGCATCATGGGCGTAAATTTGT

TTGCTGGCAAATTCTACCACTGTATTAACACCACAACCTGGTGACAGGTTTGACATCG
 AAGACGTGAATAATCATACTGATTGCCTAAACTAATAGAAAGAAATGAGACTGCT
 CGATGGAAAAATGTGAAAGTAACTTTGATAATGTAGGATTTGGGTATCTCTCTTTG
 CTTCAAGTTGCCACATTCAAAGGATGGATGGATATAATGTATGCAGCAGTTGATTCC
 AGAAATGTGGAACCTCCAGCCTAAGTATGAAGAAAGTCTGTACATGTATCTTTACTTT
 GTTATTTTCATCATCTTTGGGTCTTCTTCACCTTGAACCTGTTTATTGGGTGTCATCAT
 AGATAATTTCAACCAGCAGAAAAAGAAGTTTGGAGGTCAAGACATCTTTATGACAG
 AAGAACAGAAGAAATACTATAATGCAATGAAAAAATTAGGATCGAAAAAACCGCA
 AAAGCCTATACCTCGACCAGGAAACAAATTTCAAGGAATGGTCTTTGACTTCGTAAC
 CAGACAAGTTTTTTGACATAAGCATCATGATTCTCATCTGTCTTAACATGGTCACAAT
 GATGGTGGAACAGATGACCAGAGTGAATATGTGACTACCATTTTGTACGCATCAA
 TCTGGTGTTTATTGTGCTATTTACTGGAGAGTGTGTACTGAACTCATCTCTCTACGC
 CATTATTATTTTACCATTGGATGGAATATTTTGGATTTTGTGGTTGTCAATTCTCTCCAT
 TGTAGGTATGTTTCTTGCCGAGCTGATAGAAAAGTATTTCTGTGTCCTTACCCTGTTC
 CGAGTGATCCGTCTTGCTAGGATTGGCCGAATCCTACGTCTGATCAAAGGAGCAAAG
 GGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCCCTTCCTGCGTTGTTTAACATCG
 GCCTCCTACTCTTCCTAGTCATGTTTCATCTACGCCATCTTTGGGATGTCCAACCTTTGC
 CTATGTTAAGAGGGGAAGTTGGGATCGATGACATGTTCAACTTTGAGACCTTTGGCAA
 CAGCATGATCTGCCTATTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTAGC
 ACCCATTCTCAACAGTAAGCCACCCGACTGTGACCCTAATAAAGTTAACCCTGGAAG
 CTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGAATTTCTTTTTTGTCAAGTTAC
 ATCATCATATCCTTCCTGGTTGTGGTGAACATGTACATCGCGGTTCATCCTGGAGAAC
 TTCAGTGTTGCTACTGAAGAAAGTGCAGAGCCTCTGAGTGAGGATGACTTT
 GAGATGTTCTATGAGGTTTGGGAGAAGTTTGATCCCGATGCAACTCAGTTCATGGAA
 TTTGAAAAATTATCTCAGTTTGCAGcTGCGCTTGAACCGCCTCTCAATCTGCCACAAC
 CAAACAAACTCCAGCTCATTGCCATGGATTGCCCCATGGTGAGTGGTGACCGGATCC
 ACTGTCTTGATATCTTATTTGCTTTTACAAAGCGGGTTCTAGGAGAGAGTGGAGAGA
 TGGATGCTCTACGAATACAGATGGAAGAGCGATTTCATGGCTTCCAATCCTTCCAAGG
 TCTCCTATCAGCCAATCACTACTACTTTTAAACGAAAAACAAGAGGAAGTATCTGCTG
 TCATTATTCAGCGTGCTTACAGACGCCACCTTTTAAAGCGAACTGTAAAACAAGCTT
 CCTTTACGTACAATAAAAAACAAATCAAAGGTGGGGCTAATCTTCTTATAAAAGAA
 GACATGATAATTGACAGAATAAATGAAAACTCTATTACAGAAAAAACTGATCTGAC
 CATGTCCACTGCAGCTTGTCCACCTTCCTATGACCGGGTGACAAAGCCAATTGTGGA
 AAAACATGAGCAAGAAGGCAAAGATGAAAAAGCCAAAGGGAAATAAatgaaaataataaa
 aataattgggtgacaaattgtttacagcctgtgaaggtgatgtttttatcaacaggactccttaggaggtcaatgccaaactgactgttttaca
 caaatctccttaaggtcagtgccataaagacagtgacccctgtcagcaactgtgactctgttaaaggggagatgaccttgacaggag
 gttactgttctactaccagctgacactgtgaagataagatgcacaatggctagtcagactgtagggaccagttcaaggggtgcaaacctgt
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 ccacctgggggggtatggcaaccacatggccctccagctacacaaagtcgtggtttgcatgaggcatgctgcacttagagatcatgcatga
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gctcagaatctcatttatgagaaccatatgtcagtggttaaagtcaaggaaattgtcaacagatctcatttattaagtcattaagcaatagttgc
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Seq. Id. No. 4 (cont'd)

Seq. in No. 5

a. exon 01 (formerly exon 00)

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Seq. in No. 6

b. exon 02 (formerly exon 01)

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Seq. in No. 7

c. exon 03 (formerly exon 02)

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Seq. in No. 8

d. exon 04 (formerly exon 03)

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 gtactcttaaaaaaactgaagagcattttatfaaagtcattcctagacaaaattacgcagcaagaggacaatgctcattggccctcaggcct
 gctggcggttatactgattatcactc

Seq. in no: 9

e. exon 05 (formerly exon 04)

gctaaatagatttcatactctgtatttcacactactcttaagacactttacgaaacaactcttggtaggaagc
tgaatttaaatttagggctacgtttcatttgatgaaattaaaatccatctgcttagtttcttttagtattatcta
ttccactgatggagtgataagaaattgggtatgctatgaaaaacactgttactttatcaaatttttggatgctgtttt
cagATACACCTTCACAGGAATATATACTTTTGAATCACTTATAAAAAATTATTGCAAGG
GGATTCTGTTTAGAAGATTTTACTTTCCTTCGGGATCCATGGAAGTGGCTCGATTTC
CTGTCATTACATTTGCGtaagtgccttbytgaaactttaagagagaacatagttggtttccatcagtgccttatgctttaagaat
aggtttgccttaccgttagaatattttgtgtgattatacattcaaactctggatttcaatttagcacaacaaaggctaaagtgaatttactatagc
atgaaggcttgcagtagt

Seq. in no: 10

f. exon 06N (formerly exon 05N)

cttataagccccatgcagtaataataaatcctgctaaaaatcttgaataattctgatttaattctacag
GTTTGTAAACAGAATTTGTAAACCTAGGCAATTTTTCAGCTCTTCGCACTTTCAGAGTC
TTGAGAGCTTTGAAAACATTTTCGGTAATTCCAGtaagaagtgattagagtaaaggataggctcttgtacc
tacagcttttcttgtgctctgttttgtgtgtgtgaactcccgccttacag

//

g. exon 06A (formerly exon 05A)

gtaagaagttagtagagtaaaggataggctcttgtacccacagcttttcttgtgctctgttttgtgtgtgtg
aactcccgccttacagGTACGTCACAGAGTTTGTGGACCTGGGCAATGTCTCGGCATTGAGAAC
ATTCAGAGTTCTCCGAGCATTGAAGACGATTTTCAGTCATTCCAGtgtagagcaaggttagataat
gagacggaccatcatgtgattcagcatccttctctgttgacattcagttttacagaaaatcaggaatcataagactaggtgttcaaagaaatg
attattatgtagacatagcttatcagcctggagtta

12

h. exon 07 (formerly exon 06)

cacgcgtgcttagccctcatagtaataagcctcctaccttcagGCCTGAAAACCATTGTGGGAGCCCTGATCCA
GTCTGTGAAGAAGCTCTCAGATGTAATGATCCTGACTGTGTTCTGTCTGAGCGTATTT
GCTCTAATTGGGCTGCAGCTGTTTCATGGGCAACCTGAGGAATAAATGTATACAATGG
CCTCCCACCAATGCTTCCTTGGAGGAACATAGTATAGAAAAGAATATAACTG
TGAATTATAATGGTACACTTATAAATGAACTGTCTTTGAGTTTGAAGTGCAT
ATATTCAAGATTCAAgtaagaattattgttatgtacatttccttaaaagtagaattggattgttgaacacaaaggataaatactt
gaggggctggatatcccatcttac

13

i. exon 08 (formerly exon 07)

cgcgcaaatacttgtgcctttgaatgaataatattttaaattactcaataaacttaaagtagaacctgaccttctg
ttctcttgagtgttttaacaatgcaaatgttcagcatagcactttctttttcaaacagGATATCATTATTTTCCTGGA
GGGTTTTTTAGATGCACTACTATGTGGAAATAGCTCTGATGCAGGgtaagtaaatattgtgtgcat
ctgtgtatattgtatgtacacaatacatatgtgtatcttt

87-10 NO: 14
j. exon 09 (formerly exon 08)

aggtgttgaaaatgcaaattatcaacaaaaatttttgtaaaatattattagaaatgctgcaccatatttaaatgatga
caccaagtagctaataagactatatgcagtcaaaagttgggaaatagattagtactatttgcacacttttattttga
aataccaaattcttctgactaggcaatatcatagcatagatcagagtaaaaaggcagcagaacgacttgtaatacttctc
ttttacccacttgagCCAATGTCCAGAGGGATATATGTGTGTGACAGCTGGTAGAAATCCCA
ATTATGGCTACACAAGCTTTGATACCTTCAGTTGGGCTTTTTTGTCTTGTTCGACTa
ATGACTCAGGACTTCTGGGAAAATCTTTATCAACTGgtgagaactaaagagccacactctccatttaagta
aaagtatacaagaaaaccaattgagttatgaaattaaaaccggatgataatagtagaaagagcagaacttgacacgagacttgagttcctct
atcctattgattataacacatactagcagagtagtgccaaggattgcaattctctccatttcttcttgctcaa

15
k. exon 10 (formerly exon 09)

ttatatctgagtttctgtagccacatgagtaaatgaaagttgagcacccttagtgaataatattgggaaataattctga
tattttgtttgcagACATTACGTGCTGCTGGGAAAACGTACATGATATTTTTTGTATTGGTCAT
TtTCTTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTGTGGTGGCCATGGCcTACG
AGGAACAGAATCAGGCCACCTTGAAGAAGCAGAACAGAAAGAGGCCGAATTTCA
GCAGATGATTGAACAGCTTAAAAAGCAACAGGAGGCAGCTCAGgtaagctgcctgctcat
ggcactgacctttatcgtctgactatagagagaagtagtctagagcgtgtgat

16
l. exon 11 (formerly exon 10a)

caaccctaattaataccaatttttaaagtaaatcaaatcccaaaaagtaaatgatttttctgttgatacatgttg
gatattttgaatacgtggtctgtggagcattaacagagacataataaatgttaccatggagcaaactaaattatctcca
aaagccctcattaggtagaagaaaaaaaatctcctcttatacttgcagagaatcttctctgtgagatgatcttcagt
cagtcaatataatttttaaagccatgcaaatacttcagcccttcaaagaaagatacagtccttcaggtgctatgtt
aaaatcatttctcttcaatagCAGGCAGCAACGGCAACTGCCTCAGAACATTCCAGAGAGCCCA
GTGCAGCAGGCAGGCTCTCAGACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAAGA
GTGCTAAGGAAAGAAGAAATCGGAGGAAGAAAAGAAAACAGAAAGAGCAGTCTGG
TGGGGAAGAGAAAGATGAGGATGAATTCCAAAAATCTGAATCTGAGGACAGCATCA
GGAGGWAAGGTTTTTCGCTTCTCCATTGAAGGGAACCGGTTGACATATGAAAAGAGG
TACTCCTCCCCACACCAGgtatggcactgctgagtttactgatgcatggttgaaaattaaaacatgggagagagggggaga
tttagaaaatggactcaggaattttatcaactgaatcaaccactgtgtgttatattaaacccatccctcttcacatagttatgcaaaaactttact
ccacagatatgtaagtctacagctcgggtgtagttaagataacaccaagttgaca

Seq. Id. No. 17 - 19

Seq. ID NO: 20

p. exon 15 (formerly exon 12)

caagccatttcacccatctgaagacctcagtttccttatctgtaaagtaataattgtatattatctacttcgcgtttcca
 caaggataaaataaataatgtatatgawagctttcatcaactacaaattgccatacaaatataagttagtaataagaat
 cattgtgggaaaatagcataagcattatgttctaagagcaaatcttatgtcatgtatgtattatctgggtgaattagat
 taattttgtttgatcttagGTTTTCACTGGGATCTTTACAGCAGAAATGTTTCTGAAAATTATTGC
 CATGGATCCTTACTATTATTTCCAAGAAGGCTGGAATATCTTTGACGGTTTTATTGTG
 ACGCTTAGCCTGGTAGAACTTGGACTCGCCAATGTGGAAGGGTTATCTGTTCTCCGT
 TCATTTTCGATTGgtaaaaaaaaaaaaaaaaaggaaccaaatcaaaaacctttctaaca
 ttcagggttctgtcatagcattgtcatagttttttgccacacaaccattaggcattgtaagttttctgtaacattgc
 attgtcaaaaacttttctacatgggaataattctcaattattaggttaccttagttcaagggcwaggtcggaaggtaa
 cggtt

Seq. ID NO: 21

q. exon 16 (formerly exon 13)

gaattctaataaccatttctaggttaaagctcaatatataatgcttttaagaatcatacaaatatataattaatctttca
 tttccagCTGCGAGATTTCAAGTTGGCAAAATCTTGGCCAACGTAAATATGCTAATAAA
 GATCATCGGCAATTCCGTGGGGGCTCTGGGAAATTTAACCCTCGTCTTGGCCATCAT
 CGTCTTCATTTTTGCCGTGGTCGGCATGCAGCTCTTTGGTAAAAGCTACAAAGATTGT
 GTCTGCAAGATCGCCAGTGATTGTCAACTCCCACGCTGGCACATGAATGACTTCTTC
 CACTCCKHCCTGATTGTGTTCCGCGTGTGTGTGGGGAGTGGATAGAGACCATGTGG
 GACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTTACTGTCTTCATGATGGTCATG
 GTGATTGGAAACCTAGCGgtatgtaccacttaagatatgcattttggaaata
 caccagcatggcacatgtatacatatgtaactaacctgcacattgtgcacatgtaccctaaaactaaagtataataaaa
 aaaaagagtataatttaattggtgactgtttgtcaaaaagaaaaaactatgattattggtttaaaagtcattacct
 tggatatattatcactttaacaacacagcaatatabcagtgcccctgcatttttataccaaattctattttgtcagtea
 ctttatcacatttttatgtgaattacaatagagtatcatattgagatgagcctaaaaggatgtgctgggaccattttat
 aaattcagagccaaggaagagagaagtct

22

r. exon 17 (formerly exon 14)

gaattctcgattgtacacatataaatctgttttcttactcatacaatttttagagttacaaaaccttagattagctc
 attcaatttcactttacgaatgggagaacttgagagcaacagaaatcatgtctttgtccaaggatgtgctattgagccag
 tcacaaattcagatcaccatcttctaactactatgctgtggtgttcccttctcatcaagttttagaacttagagtttt
 tccacacttaaaagaagaataagtgattgtaatctgcttctccctacattggtgtaaaattataatcatgtttttgtg
 ttttaagGTCCTGAATCTCTTTCTGGCCTTGCTTCTGAGCTCATTTAGTGCAGACAACCTT
 GCAGCCACTGATGATGATAATGAAATGAATAATCTCCAAATTGCTGTGGATAGGATG
 CACAAAGGAGTAGCTTATGTGAAAAGAAAAATATATGARTTTATTCAACAGTCCTTC
 ATTAGGAAACAAAAGATTTTAGATGAAATTAAACCACTTGATGATCTAAACAACAA
 GAAAGACAGTTGTATGTCCAATCATAACAGCAGAAATTGGGAAAGATCTTGACTATCT
 TAAAGATGTAAATGGAACACTACAAGTGGTATAGGAACTGGCAGCAGTGTTGAAAAAT
 ACATTATTGATGAAAGTGATTACATGTCATTCATAAACAACCCCAGTCTTACTGT
 GACTGTACCAATTGCTGTAGGAGAATCTGACTTTGAaAATTTAaACACGGAAGACTTT
 AGTAGTGAATCGGATCTGGAAGaAGCAAAGAGgtaagattctataggtgtgggttaggtatgaatacatatac
 atatatatacatatacacatacatagatgaycctcagcttaatgatgttttacttaaga

Seq. Id. No. 23

s. exon 18 (formerly exon 15)

aagcttacattgtgaattatggtaaaagggttagcacagacaatgattttctattttctcccttattcaatctctctt
 ttctctaaaaatatctctacctaagaagaataaaaaacaaattcatagtaataatccttctggcaggcaacttatta
 ccaaaattaaggactttactttctatgtccatctcacttacagAAACTGAATGAAAGCAGTAGCTCATCAGAAGG
 TAGCACTGTGGACATCGGCGCACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAG
 AAACTCTTGAAcccgAAGCTTGTTCCTGAAAGtaaaagaaaagaatcctaagttaatctttcatttggagtga
 gcttatttagctgttggcagctaanataatcacatataataaaatngcactttgtaatagatataattcaatcacctctaataatnttgacagacaa
 aaaaacttaaagtctagtgtcatgctttgattatctgcccataatntgg

²⁴
 t. exon 19 (formerly exon 16)

ccatttaaatgtggctgaatgtttccacaacttcacacagctgatgaatgtgctcttactactctaggcttagagagcta
 tgctagcaagacagagatgagcatagtaataaaaagacaagacaaggacattgctaaggatattatggaagcagagaca
 ctttactacttttattcaacactttctgcagGCTGTGTACAAAGATTCAAGTGTTGTCAAATCAATGTGG
 AAGAAGGCAGAGGAAAACAATGGTGGAACCTGAGAAGGACGTGTTTCCGAATAGTT
 GAACATAACTGGTTTGAGACCTTCATTGTTTTTCATGATTCTCCTTAGTAGTGGTGCTC
 TGgtgagtgaagattaagaaaagggtgatacagcactaattttagaacactctaatactgatgacttattaatcctttgttcattgtcttagtatcca
 atgcatttttaattatcccacttgtatcttctatagatttactctataactctatatttctggattaacttttactatgtatgtaaatataaatttaagaagc
 taatcatttaattttgcttactattaaatagcccagaaagtgtagcccttcagcttattcattaacaccaaaaggatgtgaatattcaattac

²⁵
 u. exon 20 (formerly exon 17)

ccacatcaggatacaacatcaagaactatttctgactaagtcaaattaattcattggaatcatacttttctttttcttc
 caccaatagcttttcccctgattaaataagtaaaagacctttgcgaggaaaaaaaagtaacagtaactactgtttct
 ctgcccctctatttccaatgaaatgtcatatgcatatgattaatttttaaatagcttatggagtataattatttttgaaa
 gctaataatgtgaacattttctttatagGCATTTGAAGATATATATATTGAYCAGCGAAAGACGATTA
 AGACGATGTTGGAATATGCTGACAAGGTTTTCTACTTACATTTTCATTCTGGAAATGCT
 TCTAAAATGGGTGGCATATGGCTATCAAACATATTTACCAATGCCTGGAGTTGGCT
 GGACTTCTTAATTGTTGATgtaggtatcggtcatattttgtctctgttcaaggtagcttgcatttattatattcaaatctacaatag
 tgagtctcagaccactatgttatgttgacagactataatarccactaaacgcataatgcaatgagagtgatcatttctggaagacaagggctaa

²⁶
 v. exon 21 (formerly exon 18)

aaaaattatacttgcgtattatagcaactacacattgaatgatgattctgtttattaattgttattattcytgtgtg
 tgcagGTTTCATTGGTCAGTTTAAACAGCAAATGCCTTGGGTACTCAGAACTTGGAGCC
 TATCAaTCTCTCAGGACACTAAGAGCTCTGAGACCTCTAAGAGCCTTATCTCGATTG
 AAGGGATGAGGgtaagaaaaatgaagaacctgaagtattgtatatagccaaaattaaactaaatttagaaaaaaggaaaa
 atgtatgcatgcaaaagggaatggcaattcttgcaaaatgctctttattgttt

Seq. Id. No. 27

w. exon 22 (formerly exon 19)

cttggttatattgcctatagttgtttcctaagtgtattgcttaagaaaaaaaaaatgaattttaagatttttgaacct
 tgcttttacatacctagaataaatagcattgatagaaaaaagaatggaaagaccagagattactagggggaatttttt
 tctttattaacagataagaattctgacttttctttttccatttgtgtattagGTGGTTGTGAATGCCCTTTTAGGAGC
 AATTCCATCCATCATGAATGTGCTTCTGGTTTGTCTTATATTCTGGCTAATTTTCAGC
 ATCATGGGCGTAAATTTGTTTGCTGGCAAATTCTACCACTGTATTAACACCACAAC
 GGTGACAGGTTTGACATCGAAGACGTGAATAATCATACTGATTGCCTAAAACTAATA
 GAAAGAAATGAGACTGCTCGATGGAAAAATGTGAAAGTAAACTTTGATAATGTAGG
 ATTTGGGTATCTCTCTTTGCTTCAAGTTgtaagtgaacactatttctctgaatattttattgtttggaataatacaaa
 ataatgacatacatctattattagttcctaagaaaagtatatatttcttctatttaaaaaatttcaattttagtagacaagttatga
 gcccatggtgtaaaactttattacatgtaaggact

28

x. exon 23 (formerly exon 20)

aatggccattttgttcaatatgtgttctagaaatgaaaagccatactaaaatactgtcttgggtccaaaatctgtgtaaaa
 ttgttttgaatgtctttcaaaaatattcccttttgaaaattatatcagtaagaatattttaaacatcagggtctaaa
 ttattttactccaaagtaaaacatgcatgtccttcttaatatGCCACATTCAAAGGATGGATGGATATAATGTA
 TGCAGCAGTTGATTCCAGAAATGtaagtattcctgtattctaagtcttttacaatattgatcagggtgtaaaattaatcgaa
 taaagcataaacgaccaaataaatgattctatcttgatttaaaatatttgggaaaaagtgtgacaggtaaatattcaagc
 atagcaatgtttatcagaaagatcttactaagataattcaacacatgaattattttg

29

y. exon 24 (formerly exon 21)

cagaaaaaaaaaaaatgctgacatattagtaagaataattttntctattgttatgaaaaagcaccagtgacgatttcag
 cactaaaatgtatggtaatatatttacaaaatattcccctttgtagGTGGAACCTCAGCCTAAGTATGAAGAAAGT
 CTGTACATGTATCTTTACTTTGTTATTTTCATCATCTTTGGGTCTTCTTCACCTTGAA
 CCTGTTTATTGGTGTTCATCATAGATAATTTCAACCAGCAGAAAAAGAAAGataagattttctaata
 atttctctcccactgagatagaaaaattattccttggagtgtttctctgccaaatgagtlacttgaatttagaacaatgggagtatattataactg

30

z. exon 25 (formerly exon 22)

gtcattttgaattatttaggggaattaaaatattatcatacctaaagagtacaattttttacatttttaaatcccagata
 taattataactaatcagttgaattttgtatttcttttttagccatccattttctattttaacattgaaaaaatgtacaaa
 aggacacagtttaaccagtttgatttttctttctatacTTTGGAGGTCAAGACATCTTTATGACAGAAGAACA
 GAAGAAATACTATAATGCAATGAAAAAATTAGGATCGAAAAAACCGCAAAAGCCTA
 TACCTCGACCAGGAgtaagaagtataaatgatatgggggaaaaatacaaaaacaaaactgcatgctgtctcacaaaaaaga
 aaagtaagctaaacattt

Seq. ID No: 31

aa. exon 26 (formerly exon 23)

ttttaacaattaattatgctataaattcattcttacaaaaatcatttggatgactactttgcaagaaactagaaagtca
 attaatgcagaaagtacttaagtctaatagcacatgagaaaaactccttgggtgtaaaagcatttctattctctacagA
 ACAAATTTCAAGGAATGGTCTTTGACTTCGTAACCAGACAAGTTTTTGACATAAGCA
 TCATGATTCTCATCTGTCTTAACATGGTCACAATGATGGTGGAAACAGATGACCAGA
 GTGAATATGTGACTACCATTTTGTACGCATCAATCTGGTGTTCATTGTGCTATTTAC
 TGGAGAGTGTGTACTGAAACTCATCTCTCTACGCCATTATTATTTTACCATTGGATGG
 AATATTTTTTGATTTTGTGGTTGTCATTCTCTCCATTGTAGGtaagaaatatttaaagttctaaattcagtta
 aataaaaagtgaagctgaacaatacaagattagattcaagatcatcccagcaatcagagataatcactgtaaatat

Seq. ID No: 32

ab. exon 27 (formerly exon 24)

agtatatattatatatagttgtcatatttaataataactgggttcaggactctgaaccttaccttggagctttagaagaaa
 catatgtttattttaacgcgatgatttcttactgggtgattctcattgtttattcatagGTATGTTTCTTGCCGAGCT
 GATAGAAAAGTATTTTCGTGTCCCCTACCCTGTTCCGAGTGATCCGTCTTGCTAGGATT
 GGCCGAATCCTACGTCTGATCAAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCT
 TTGATGATGTCCCTTCCTGCGTTGTTTAACATCGGCCTCCTACTCTTCCTAGTCATGTT
 CATCTACGCCATCTTTGGGATGTCCAACCTTGCCTATGTTAAGAGGGGAAGTTGGGAT
 CGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATGATCTGCCTATTCCAAAT
 TACAACCTCTGCTGGCTGGGATGGATTGCTAGCACCCATTCTCAACAGTAAGCCACC
 CGACTGTGACCCTAATAAAGTTAACCCTGGAAGCTCAGTTAAGGGAGACTGTGGG
 AACCCATCTGTTGGAATTTTCTTTTTTGTGTCAGTTACATCATCATATCCTTCCTGGTTGT
 GGTGAACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAAGAAAG
 TGCAGAGCCTCTGAGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGGAGAAGTT
 TGATCCCGATGCAACTCAGTTCATGGAATTTGAAAAATTATCTCAGTTTGCAGTGCG
 CTTGAACCGCCTCTCAATCTGCCACAACCAAACAACTCCAGCTCATTGCCATGGAT
 TTGCCCATGGTGAGTGGTGACCGGATCCACTGTCCTTGATATCTTATTTGCTTTTACAA
 AGCGGGTTCTAGGAGAGAGTGGAGAGATGGATGCTCTACGAATACAGATGGAAGA
 GCGATTGATGGCTTCCAATCCTTCCAAGGTCTCCTATCAGCCAATCACTACTACTTTA
 AAACGAAAACAAGAGGAAGTATCTGCTGTCATTATTCAGCGTGCTTACAGACGCCA
 CCTTTTAAAGCGAACTGTAAAACAAGCTTCCTTTACGTACAATAAAAACAAAATCAA
 AGGTGGGGGCTAATCTTCTTATAAAAGAAGACATGATAATTGACAGAATAAATGAAA
 ACTCTATTACAGAAAAAACTGATCTGACCATGTCCACTGCAGCTTGTCCACCTTCCT
 ATGACCGGGTGACAAAGCCAATTGTGGAAAAACATGAGCAAGAAGGCCAAAGATGA

AAAAGCCAAAGGGAAATAAATGAAAATAAATAAAAAATAATTGGGTGACAAATTGTT
 TACAGCCTGTGAAGGTGATGTATTTTTATCAACAGGACTCCTTTAGGAGGTCAATGC
 CAAACTGACTGTTTTTACACAAATCTCCTTAAGGTCAGTGCCTACAATAAGACAGTG
 ACCCCTTGTCAGCAAACCTGTGACTCTGTGTAAAGGGGAGATGACCTTGACAGGAGG
 TTAGTGTTCTCACTACCAGCTGACACTGCTGAAGATAAGATGCACAATGGCTAGTCA
 GACTGTAGGGACCAGTTTCAAGGGGTGCAAACCTGTGATTTTGGGGTTGTTAACAT
 GAAACACTTTAGTGTAGTAATTGTATCCACTGTTTGCATTTCAACTGCCACATTTGTC
 ACATTTTTATGGAATCTGTTAGTGGATTCATCTTTTTGTTAATCCATGTGTTTATTATA
 TGTGACTATTTTTGTAAACGAAGTTTCTGTTGAGAAATAGGCTAAGGACCTCTATAA
 CAGGTATGCCACCTGGGGGGTATGGCAACCACATGGCCCTCCCAGCTACACAAAGT
 CGTGGTTTGCATGAGGGCATGCTGCACTTAGAGATCATGCATGAGAAAAAGTCACA
 AGAAAAACAAATTCTTAAATTTACCATAATTTCTGGGAGGGGTAAATTGGGTGATAAG
 TGGAGGTGCTTTGTTGATCTTGTTTTGCGAAATCCAGCCCCTAGACCAAGTAGATTA
 TTTGTGGGTAGGCCAGTAAATCTTAGCAGGTGCAAACCTTCATTCAAATGTTTGGAGT
 CATAAATGTTATGTTTCTTTTTGTTGTATTAACAAAAAACCTGAATAGTGAATATTG
 CCCCTCACCTCCACCGCCAGAAGACTGAATTGACCAAATTAATCTTTATAAATTT
 CTGCTTTTTCTGCACTTTGTTTAGCCATCTTCGGCTCTCAGCAAGGTTGACACTGTA
 TATGTTAATGAAATGCTATTTATTATGTAAATAGTCATTTTACCCTGTGGTGCACGTT
 TGAGCAAACAAATAATGACCTAAGCACAGTATTTATTGCATCAAATATGTACCACAA
 GAAATGTAGAGTGCAAGCTTTACACAGGTAATAAAATGTATTCTGTACCATTATAG
 ATAGTTTGGATGCTATCAATGCATGTTTATATTACCATGCTGCTGTATCTGGTTTCTC
 TCACTGCTCAGAATCTCATTTATGAGAAACCATATGTCAGTGGTAAAGTCAAGGAAA
 TTGTTCAACAGATCTCATTTATTTAAGTCATTAAGCAATAGTTTGCAGCACTTTAACA
 GCTTTTTGGTTATTTTTACATTTTAAGTGGATAACATATGGTATATAGCCAGACTGTA
 CAGACATGTTTAAAAAACACACTGCTTAACCTATTAAATATGTGTTTAGAATTTTA
 TAAGCAAATATAAATACTGTAAAAAGTCACTTTATTTTATTTTTTCAGCATTATGTACA
 TAAATATGAAGAGGAAATTATCTTCAGGTTGATATCACAATCACTTTTCTTACTTTCT
 GTCCATAGTACTTTTTTCATGAAAGAAATTTGCTAAATAAGACATGAAAACAAGACTG
 GGTAGTTGTAGATTTCTGCTTTTTAAATTACATTTGCTAATTTTAGATTATTTACAA
 TTTTAAGGAGCAAATAGGTTTCACGATTCATATCCAAATTATGCTTTGCAATTGGAA
 AAGGGTTTAAATTTTATTTATATTTCTGGTAGTACCTGCACTAACTGAATTGAAGGT
 AGTGCTTATGTTATTTTTGTTCTTTTTCTGACTTCGGTTTATGTTTTCATTTCTTTGG
 AGTAATGCTGCTCTAGATTGTTCTAAATAGAATGTGGGCTTCATAATTTTTTTTCCA
 CAAAAACAGAGTAGTCAACTTATATAGTCAATTACATCAGGACATTTTGTGTTTCTT
 ACAGAAGCAAACCATAGGCTCCTCTTTTCTTAAACTACTTAGATAAACTGTATTC
 GTGAAGTGCATGCTGGAAAAATGCTACTATTATGCTAAATAATGCTAACCAACATTTA
 AAATGTGCAAACTAATAAAGATTACATTTTTTATTTTA

ttcttggtgccagcttatcaatcccaaactctgggtgtaaaagattctacagggcactttcttatgcaaggagctaaaca
gtgattaaggagcaggatgaaaagATGGCACAGTCAGTGCTGGTACCGCCAGGACCTGACAGCTT
CCGCTTCTTTACCA
GGGAATCCCTTGCTGCTATTGAACAACGCATTGCAGAAGAGAAAGCTAAGAGACCC
AAACAGGAACGCAAGGATGAGGAT
GATGAAAATGGCCCAAAGCCAAACAGTGACTTGGAAGCAGGAAAATCTCTTCCATT
TATTTATGGAGACATTCCTCCAGA
GATGGTGTCAGTGCCCCTGGAGGATCTGGACCCCTACTATATCAATAAGAAAACGTT
TATAGTATTGAATAAAGGGAAAG
CAATCTCTCGATTCAGTGCCACCCCTGCCCTTTACATTTTAACTCCCTTCAACCCTAT
TAGAAAATTAGCTATTAAGATT
TTGGTACATTCTTTATTCAATATGCTCATTATGTGCACGATTCTTACCAACTGTGTAT
TTATGACCATGAGTAACCCCTCC
AGACTGGACAAAGAATGTGGAGTATACCTTTACAGGAATTTATACTTTTGAATCACT
TATTAATACTTGCAAGGGGCT
TTTGTTTAGAAGATTTTACATTTTACGGGATCCATGGAATTGGTTGGATTTTACAGT
CATTACTTTTGCATATGTGACA
GAGTTTGTGGACCTGGGCAATGTCTCAGCGTTGAGAACATTCAGAGTTCTCCGAGCA
TTGAAAACAATTTTCAATGTCATTCC
AGGCCTGAAGACCATTGTGGGGGCCCTGATCCAGTCAGTGAAGAAGCTTTCTGATGT
CATGATCTTGACTGTGTTCTGTC
TAAGCGTGTTTGGCGCTAATAGGATTGCAGTTGTTTCATGGGCAACCTACGAAATAAAT
GTTTGCAATGGCCTCCAGATAAT
TCTTCCTTTGAAATAAATATCACTTCCTTCTTTAACAATTCATTGGATGGGAATGGTA
CTACTTTCAATAGGACAGTGAG
CATATTTAACTGGGATGAATATATTGAGGATAAAAGTCACTTTTATTTTTTAGAGGG
GCAAAATGATGCTCTGCTTTGTG
GCAACAGCTCAGATGCAGGCCAGTGTCTGAAGGATACATCTGTGTGAAGGCTGGT
AGAAACCCCACTATGGCTACACG
AGCTTTGACACCTTTAGTTGGGCCTTTTGTCTTATTTCGTCTCATGACTCAAGACT
TCTGGGAAAACCTTTATCAACT
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SIRGSLFSPRRNSRASLFSFRGRAKDIGSENDFADEHSTFEDNDSRRDSLFPVPHRHGERR
HSNVSQASRASRVLPILPM
NGKMHSVAVDCNGVVSLVGGPSTLTSAGQLLEGGTTTETEIRKRSSSYHVSMDLLEDPT
SRQRAMSIALTNTMEELEE
SRQKCPPCWYKFANMCLIWDCCKPWLKVHLLVNLVMDPFVDLAITICIVLNTLFMAM
EHYPMTEQFSSVLSVGNLVFTG
IFTAEMFLKIIAMDPYYYFQEGWNIFDGFIVSLSLMELGLANVEGLSVLRSFRLLRVFKLA
KSWPTLNMLIKIIGNSVGA
LGNLTLVLAIVFIFAVVGMQLFGKSYKECVCKISNDCELPRWHMHDFHSLIVFRVLC
GEWIETMWDCMEVAGQTMCL
TVFMMVMVIGNLVVLNLFLALLSSFSNDLAATDDDNEMNNLQIAVGRMQKGIDFVK
RKIREFIQKAFVRKQKALDEIK
PLEDLNKKDSCISNHTTIEIGKDLNYLKDGNNGTTSIGIGSSVEKYVVDESDYMSFINNPSL
TVTVPIAVGESDFENLNT
EFSSESDMEESKEKLNATSSSEGSTVDIGAPAEGEQPEVEPEESLEPEACFTEDCVRKFKC
CQISIEEGKGKLWWNLRKT
CYKIVEHNWFETFIVFMILLSSGALAFEDIYEQRKTIKTMLEYADKVFTYIFILEMLLKW
VAYGFQVYFTNAWCWLDL
IVDVSLVSLTANALGYSELGAIKSLRTLRLRPLRLRSRFEGRMRAVVNALLGAIPSIMNV
LLVCLIFWLIFSIMGVNLFA
GKFYHCINYTTGEMFDVSVVNNYSECKALIESNQATARWKNVKVNFNDNVGLGYLSLLQV
ATFKGWMDIMYAAVDSRNVELQ
PKYEDNLYMYLYFVIFHIFSFFTLNLFIGVIIDNFNQQKKKFGGQDIFMTEEQKKYYNAM
KKLGSKKPQKPIPRPANKF

QGMVDFVTKQVFDISIMILICLNMVTMMVETDDQSQEMTNILYWINLVFIVLFTGECVL
KLISLRYYYFTIGWNIFDFV
VVILSIVGMFLAELIEKYFVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNI
GLLLFLVMFIYAIFGMS
NFAYVKREVGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSGPPDCDPDKDHPGS
SVKGDCGNPSVGIFFFVSYI
IISFLVVVNMYIAVILENFSVATEESAEPLEDDFEMFYEVWEKFDPDATQFIEFAKLSD
ADALDPPLLIAPNKVQLI
AMDLPVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEERFMASNP SKVSYEPITTTL
KRKQEEVSAIIIQRAYRRYL
LKQKVKKVSSIYKKDKGKECDGTPIKEDTLIDKLNENSTPEKTDMPSTTSPPSYDSVT
PEKEKFEKDKSEKEDKGKDI
RESKK.

Seq. Id. No. 35 (cont'd)

MAQSVLVPPGPDSFRFFTRESLAAIEQRIAEKAKRPKQERKDEDDENGPKPNSDLEAGK
SLPFIYGDIPPEMVSVPLED
LDPYYINKKTFIVLNKGKAISRFSATPALYILTPFNPIRKLAIKILVHSLFNMLIMCTILTNC
VFMTMSNPPDWTKNVEY
TFTGIYTFESLIKILARGFCLEDFTLRDPWNWLDFTVITFA YVTEFVN LGNV SALRTFRV
LRALKTISVIPGLKTIVGA
LIQSVKKLS DVMILTVFCLSVFALIGLQLFMGNLRNKCLQWPPDNSSFEINITSFNNSLD
GNGTTFNRTVSIFNWDEYI
EDKSHFYFLEGQNDALLCGNSSDAGQCPEGYICVKAGRNP NYGYTSFDTFSWAFLSLFR
LMTQDFWENLYQLTLRAAGKT
YMIFFVLVIFLGSFYLINLILAVVAMAYEEQNQATLEEAQEKEAEFQQMLEQLKKQEE
AQAAAAASAESRDFSGAGGI
GVFSESSSVASKLSSKSEKELKNRRKKKKQKEQSGEEKNDRVLKSESEDSIRRKGRFS
LEGSRLTYEKRFSSPHQSL
SIRGSLFSPRRNSRASLSFRGRAKDIGSEND FADDEHSTFEDNDSRRDSL FVPHRHGERR
HSNVSQASRASRVLPILPM
NGKMHS AVDCNGVVS LVGGPSTLTSAGQLLPEGTTTETEIRKRRSSSYHVSMDLLEDPT
SRQRAMS IASILTNTMEELEE
SRQKCPPCWYKFANMCLIWDCKPWLKV KHLVNLVVMDFVDLAITICIVLNTLFMAM
EHYPMTEQFSSVLSVGNLVFTG
IFTAEMFLKIIAMDPY YFQEGWNIFDGFIVSLSLMELGLANVEGLSVLRSFRLLRVFKLA
KSWPTLNMLIKIIGNSVGA
LGNLT LVLAIVFIFAVVGMQLFGKSYKECVCKISNDCELPRWHMHDFH SFLIVFRVLC
GEWIETMWDCMEVAGQTMCL
TVFMMVMVIGNLVVLNLFALLSSFS DNLAATDDDNEMNNLQIAVGRMQKGIDFVK
RKIREFIQKAFVRKQKALDEIK
PLEDLNNKKDSCISNHTTIEIGKDLNYLKDGN GTTSGIGSSVEKYV VDESDYMSFINNPSL
TVTVPIAVGESDFENLNT
EFSSESDMEESKEKLNATSSSEGSTVDIGAPAEGEQPEVEPEESLEPEACFTEDCVRKFKC
CQISIEEGKGKLWWNL RKT
CYKIVEHNWFETFIVFMILLSSGALAFEDIYEQRKTIKTMLEYADKVFTYIFILEMLLKW
VAYGFQVYFTNAWCWLDL
IVDVSLVSLTANALGYSELGAIKSLRTLRLRPLRLSRFEGMRVAVVNALLGAIPSIMNV
LLVCLIFWLIFSIMGVNLFA
GKFYHCINYTTGEMFDVSVVNNYSECKALIESNQ TARWKNVKVNFDNVGLGYLSLLQV
ATFKGWMDIMYAAVDSRNVELQ
PKYEDNLYMYLYFVIFIIFGSFFT LNLFIGVIIDNFNQQKKKFGGQDIFMTEEQKKYYNAM
KKLGSKKPQKPIRPANKF

QGMVDFDVTKQVFDISIMILICLNMVTMMVETDDQSQEMTNILYWINLVFIVLFTGECVL
KLISLRYYYFTIGWNIFDFV
VVILSIVGMFLAELIEKYFVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNI
GLLLFLVMFIYAIFGMS
NFAYVKREVGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSGPPDCDPDKDHPGS
SVKGDCGNPSVGIFFFVSYI
IISFLVVVNMYIAVILENFSVATEESAEPLEDDFEMFYEVWEKFDPDATQFIEFAKLSDF
ADALDPPLLIAPNKVQLI
AMDLPMVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEERFMASNP SKVSYEPITTTL
KRKQEEVSAIIIQRAYRRYL
LKQKVKKVSSIIYKKDKGKECDGTPIKEDTLIDKLNENSTPEKTDMPSTTSPPSYDSVTK
PEKEKFEKDKSEKEDKGKDI
RESKK.

Seq. Id. No. 36 (cont'd)

Seq. Id. No. 37

a. exon 01 (formerly exon 00)

gaattctttatatgggtgaatgactttctgacatagcaataaaaaagcatgaggagaagcattatctgttaacaaaatt
aacacttaaaatcaacaaagtttaattgttctgccaagaaaagcctgtggaagatcagttccacaactgagagcttgg
ggctgcttcagacatatgtctgtgtgtacgctgtgaagggtttctcttcacagttccccgccctctagtggtagttaca
ataatgccatttttagtccctgtacaggaatgcctctcttacttcagttaccagaatccttttacaggaagttaggt
gtggctttgaaggagaattaaaaaaaaaaaaaaaaaaaaaagatttttttttaaaagcatgatggaatttta
gctgcagtcTTCTTGGGGGCCAGCTTATCAATCCCAAACCTCTGGGGGTAAAAGATTCTACA
GGGgtaagtgtttattatc
ttattatgcttattctgtgtatgcttcttacctttacagtagtagaatccttggggaaatctgcagagggaccacttt
cattttgaagctgctggctgcatgttttagcatgtctcttattagagaatccaggcatggcagtttctccccagtg
tgcaaggaccattctcatgcctatgtctgtcgttaggcagtgagggtctctaggaatgggtgaaaaaatgagggatgttt
tggaggcactataactggggagggcagctctgctagctggtagctgaaggctcctggtttacttcaacatttttttaa
ataaaactgtgcagtagttttgtatttttaggggtccctctgtttatctgggtatgctgcagaagtgaactgcataa
cacatttcaactcttagaaatgcattccatata

exon 02 (formerly exon 01)

ctcagtgcatgtaactgacacaatcacctctatctaattggtcatgcttcttacctctgttctgtagCACTtTCTTATGC
AAGGAGCTAAACAGTGATTAAAGGAGCAGGATGAAaAGATGGCACAGTCAGTGCTG
GTACCGCCAGGACCTGACAGCTTC
CGCTTCTTTACCAGGGAATCCCTTGCTGCTATTGAACAACGCATTGCAGAAGAGAAA
GCTAAGAGACCCAAACAGGAACG
CAAGGATGAGGATGATGAAAATGGCCCAAAGCCAAACAGTGACTTGGAAGCAGSAA
AATCTCTTCCATTTATTTATGGAG
ACATTCCTCCAGAGATGGTGTGAGTGCCCTGGAGGATCTGGACCCCTACTATATCA
ATAAGAAAgtagtcttagtca
agttgccttcaactgcctatttactaattgttctgggctagtcaggatgatgggaagaaggctggcctccttccct
ctgtctaaagtatcactaagatgctggatgggcctgaccgtgtaattggaccaatgatcctagaagcttttgaagcact
catttgaacctgcatttgtgagacaggcagagaactggtgaggcatcctccagcgcggaattaaggaaggacaaaagcc
tattcaccttctgaatacaaatatattatgcttaaccagtgtaattgacctgattccctaataatgttgagaagcaaa
aa

exon 03 (formerly exon 02)

cctatggcattgatcacaaattttcttaataatcctcatgtcatttatcaaatttaggaaagtattatgtctcagaaaa
aaaaagcatctatcttcatgtcatatgatgtaattattatgtttacactattttacagggaatattataaataatg
gttttacttttcttaaaatattcttaatatatattctaaagttttgtttatgtgtgttttcttttcagACGTTT
ATAGTATTGAATAAAGGGAAAGCAATCTCTCGATTGAGTCCACCCCTGCCCTTTAC
ATTTAACTCCCTTCAACCCTAT
TAGAAAATTAGCTATTAAGATTTTGGTACATTCatataccttttcaaactgcacttaatatgattttcttcttgac
ca
agttattgagctacacattttccaaaatattctgtggttggaatgttatgtgttcttttttcttcttactcaa
tcgttagcatgttgcaaaatgagatcacaggtaagtgaatttcttccccgtcttctaagtgttcttcttaccact

40

exon 04 (formerly exon 03)

acctaaatagcctcaaaatagttgatggcttggcctgaagacaagatctaaatatgaggttgctgagttatagaaatggc
 aaaaaaagggtcaataatagaataaagcaacaaaataatagtaagcactaaagtttaacttcattggtggtgaagg
 catggtagtgcataaaagtaagattttccattgaactttgtcttccttgacgatattctacTTTATTCAATATGCTCAT
 TATGTGCACGATTCTTACCAACTGTGTATTTATGACCATGAGTAACCCTCCAGACTG
 GACAAAGAATGTGGAGtaagtat
 aaatattttcaatattgacctccctttatgtttcatattgtgcttttaacaccttgagacctcctcaatttcttaaca
 aatcatgctagctactgttaaccagacctgattcaattcatttctgtcactaaatgtcttctaggacaaagcttgtag
 tgggctcacttagttgtgtaattactgca

41

exon 05 (formerly exon 04)

taagatatgtacttgtaaattaaccactagatttttaatgtgagcttggctattgtctctcagGTATACCTTTACAGGAA
 TTTATACTTTTGAATCACTTATTTAAAATACTTGCAAGGGGCTTTTGTTTAGAAGATT
 CACATTTTACGGGATCCATGG
 AATTGGTTGGATTTACAGTCATTACTTTTGCgtaagtatcttaatacattttctatcctggaagagtaaatcactggtg
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 caaattatccagtttgagaaattaggaactatcatagtaaattacatgg

42

exon 06N (formerly exon 05N)

caattagcactgtaaagtaataaaagttcccaataacagagattatgattgatgacaatgccattttcctctaattgg
 gaaagctgatggcgacactcatgaaattaaaaaggtcttgatgaagaccaangaagacgtagattccctaaattctga
 ataactctgatttaattctacagGTATGTAAACAGAATTTGTAAACCTAGGCAATGTTTCAGCTCTTC
 GAACTTTCAGAGT
 CTTGAGAGCTTTGAAAACCTATTTCTGTAATTCCAGgtaagaagaaaatggataaggtggttaggcccttat
 atctcaa
 ctgtttctgtgttctgtcattgtgtttgtgtgaacccccctattacag

43

exon 06A (formerly exon 05A)

gtaagaagaaaatggataaggtggttaggcccttatatctccaactgtttcttgtgtctgtcattgtgtttgtgtgtg
 aacccccctattacagATATGTGACAGAGTTTGTGGACCTGGGCAATGTCTCAGCGTTGAGAAC
 ATTCAGAGTTCTCCGAG
 CATTGAAAACAATTTACAGTCATTCCAGgtgagagctagggttaaacaccgaggctgactttagctacagtgggtgctacaat
 cacagcttttgtgcagaagccttgtgtcagttgcatattgcaataaatatgtaaaaaagcaagaattggtacatcatt
 ttttgatggatttgattcttgccttttaccctgtgttctttaaactattctaaatcagcctttgagttaacaag
 tgttgcatga

Seq. in No. 44

exon 07 (formerly exon 06)

aaagagtgttggaaatacacatttgggttcattccattcacagtttctaatgaacatacaagttctgcttcattcat
 tttaccagctagtaggcttttcatgaaatgttattcaatcacaacattaaactaatattgttggcattctgcatgac
 atttttattttccaggccaagctcatgatattttgcccgtaaaatagctgtgagtagtatattaantcccccttct
 gattttgtttgtagGCCTGAAGACCATTGTGGGGGCCCTGATCCAGTCAGTGAAGAAGCTTTC
 TGATGTCATGATCTTGA
 CTGTGTTCTGTCTAAGCGTGTTTGCCTAATAGGATTGCAGTTGTTTCATGGGCAACCT
 ACGAAATAAATGTTTGCAATGG
 CCTCCAGATAATTCTTCCTTTGAAATAAATATCACTTCCTTCTTTAACAATTCATTGG
 ATGGGAATGGTACTACTTTCAA
 TAGGACAGTGAGCATATTTAACTGGGATGAATATATTGAGGATAAAAgtagatatactctata
 aaccattaagttgtt
 agttctctaaatattaaatattatataatggaaattatctcaatttagatgtgaatcaagtacttagactaatttaa
 gatgatttaatacatataaaagagatatcaaggataccttattctatttttsttctgtccattgatagtaaagt
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 ctagagaaaccatttatcaagatgaataagaatttgtgtctcctcagaaggtaagtaaccctgatttagccattcac
 ttcatecatattctaattagtcctt

45
exon 08 (formerly exon 07)

gttcaattattgtgaaaaatcttcttttagccatatatttatttagtttatccatctcattatgattgaaaacatttgtg
 agctttgccacctaacaggggtggtgaagtgtttacaggatttaattgattcttctatttcttctttaaagG
 TCACTTTTATTTTTTACAGGGGCAAAATGATGCTCTGCTTTGTGGCAACAGCTCAGAT
 GCAGGgtaagtgtatgcttct
 actgagtttcagtcacactgtccatcagtgtaataaacctgccacctcccactcatccagtcaccactcctcactc
 aaaacctccataaattctacttcacgggtgactctcagaatgaccaggataagtgtagattctca

46
exon 09 (formerly exon 08)

tataataatgacaattatgaatcacagaggaatccacaaagtagaccttatagattctgtcattatataaatcagtcac
 ttagtgctgagtttaagtactgggtaaggtgagagaaatcggtttttctagtgctgtataaaacagacattggcatat
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 TGAAGGATACATCTGTGTGAAGGCTGGTAGAAACCCCAACTATGGCTACACGAGCT
 TTGACACCTTTAGTTGGGCCTTTT
 TGTCTTATTTTCGTCTCATGACTCAAGACTTCTGGGAAAACCTTTATCAACTGgtgagaac
 agataaaatcattttctg
 agaatacataaaacaccgaactcaagagaat

Seq. Id. No. 47
 exon 10 (formerly exon 09)

tgctgtagaatatttttacttagagtgtaagttgtaacatcctatataaaattttataaaatctcttccatttg
 cagACACTACGTGCTGCTGGGAAAACGTACATGATATTTTTTGTGCTGGTCATTTTCTT
 GGGCTCATTCTATCTAATAAA
 TTTGATCTTGGCTGTGGTGGCCATGGCCTATGAGGAACAGAATCAGGCCACATTGGA
 AGAGGCTGAACAGAAGGAAGCTG
 AATTTTCAGCAGATGCTCGAACAGTTGAAAAAGCAACAAGAAGAAGCTCAGgtatagtga
 caagcatacggctcttgg
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 tggcatcaaaaaatggataattataattgctttactgacatttttttccctgtgactccttgaggaaattaatgatt
 aacaaaggcctcatgtactcaaacctgcagagtagataaacctacatgtcctcagttgaagtattttcttaggggaagag
 gaattc

48
 exon 11 (formerly exon 10a)

tatgtatcatcttccatgaatgcgcattttactctttgattggtctaataacagtgtactgtgttctaaacacagaa
 taaaatggagaattgttttcaagattatcttcatgatattgaagctcaattaagcagtaacatgataattttttaa
 gatnatatgcaacttcccacatactttgcgcccttctagGCGGCAGCTGCAGCCGCATCTGCTGAATCAAGA
 GACTTCAG
 TGGTGCTGGTGGGATAGGAGTTTTTTTCAGAGAGTTCTTCAGTAGCATCTAAGTTGAG
 CTCCAAAAGTGAAAAAGAGCTGA
 AAAACAGAAGAAAGAAAAAGAAACAGAAAGAACAGTCTGGAGAAGAAGAGAAAA
 ATGACAGAGTCCTAAAATCGGAATCT
 GAAGACAGCATAAGAAGAAAAGGTTTCCGTTTTTCCTTGGAAGGAAGTAGGCTGAC
 ATATGAAAAGAGATTTTCTTCTCC
 ACACCAGgtaaaaatattaaattacatgaattgtgttctcataaatttttaaaagaatatgccagaatttaaggagag
 aaaaccgccttccactggatggcacaatgcttcagagtagtgatgattatcaagtgtttggctatcacttcagagaa
 tttgtgagttttgcaacttttggaatcccaggaaggaaatttttagatccctctgggtttggaaaaatttg

49
 exon 12 (formerly exon 10b)

ttatggggacacttctgactatgttgaggtgtgggtaaagtaggagaaaagagagcagaagatggaaaatggaggaagga
 gaaaaagcgagagtgaaatagaaaaggtgaacctgtagaagtgccaaaatgccaccagcagtcacagaggggtgctt
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 GCTGATGATGAGCACAGCACCTTTGAGGACAATGACAGCCGAAGAGACTCTCTGTT
 CGTGCCGCACAGACATGGAGAACG

GCGCCACAGCAATGTCAGCCAGGCCAGCCGTGCCTCCAGGGTGCTCCCCATCCTGCC
 CATGAATGGGAAGATGCATAGCG
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 CTGGGCAGCTCCTACCAGAGgtg

aggccaacyymagattgcagctgatgtgaagagagttgtgactgggtgcaggcaggagtggtttccattmcacatctaa
 gaatttkttgagtttstgcccaggctgggagttgttcaatcaagctgttaactgtcttgtaaactsttctattca
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 aaattaatgctcacaaattaaataacttaaggatttgtgattgtgttcatttaaaggaga

50

exon 13 (formerly exon 10c)

ataggaaagcccaccttgacaaccagggtccccaaaagctgaaaatctgacagactttaacaacccccaaataatt
 atcattccaacaatatcttagtgagctttttacatctgagaaagcatgggtatatttagttaataacacctgttgtag
 gaatgctttggcctttgctgctttcaaaaatagtggttatttcatctgaaattctactcttagGGCACAACACTACTGAAAC
 AGAAATAAGAAAGAGACGGTCCAGTTCTTATCATGTTTCCATGGATTATTATTGGAAGA
 TCCTACATCAAGGCCAAAGAGCAA
 TGAGTATAGCCAGTATTTTGACCAACACCATGGAAGgtatgttaaaagtcctgcgtcacagtacttggtg
 ctttctctaa
 tgatgaaaaacacttcataaatttcaataaaaacttcctgacttgatattgtatcattattacacattttactaaataa
 cagtaaaatccgtgcataactcatggattcatatattccacagatttttttttatatttagcctgtagaaagctgct
 gcaaatgtaaggatatatttgaaacaccacttcataacttaa

51

exon 14 (formerly exon 11)

gcttactagcctttctgtactgatcctttctatgacagcaaaccattgtaaaattttccctgttctccagcagattaa
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 tttcatgaggattctaacttttttctccagAACTTGAAGAATCCAGACAGAAATGCCCCACCATGCTGGT
 ATAAATTT
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 GTCAACCTGGTTGTAATGGACCC
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 GAGCACTATCCCATGACGGAGC
 AGTTCAGCAGTGTACTGTCTGTTGGAAACCTGgtaagcctcactgagagtttcttctctctgaaagagttataattg
 ccttagtgaattttacatattgctctcaaatataatcaactaattggccatgtatatcttgacatcaaatgttttagca
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 aattt

52

exon 15 (formerly exon 12)

tggcccaaaccaatttttaaatcaggaatttaattwtatattgttgggagttaaattaagttgctcaataattattcgt
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 TTC
 TCAAGATAATTGCCATGGATCCATATTATTACTTTCAAGAAGGCTGGAATATTTTTG
 ATGGTTTTATTGTGAGCCTTAGT
 TTAATGGAACCTGGTTTGGCAAATGTGGAAGGATTGTCAGTTCTCCGATCATTCCGG
 CTGgtaaattaactgggagtggt
 cataaaatgtactttrtaattaattagcttcattctcatctagtaaaaatggcaagattcccatcattataatatt
 tgaatacxcttctaaaacagattggattgccataccaccaaatggtagttcttctcatcatagctttaataaagtcca
 cttaaa

53

exon 16 (formerly exon 13)

acagatttctcctgtgtccatgtgactaaccxcattgtgcacatgtaccctaaaaaxtagtatataataataaaaaaa
 aataaaaaataaxaaataaaaaataaaaaataaaaaattgcagatttttagaaatgcagagxattaacactgttct
 tgettttatttccagCTCCGAGTTTTCAAGTTGGCAAATCTTGGCCAACTCTAAATATGCTAA
 TTAAGATCATTGGCAA
 TTCTGTGGGGGCTCTAGGAAACCTCACCTTGGTATTGGCCATCATCGTCTTCATTTTT
 GCTGTGGTTCGGCATGCAGCTCT
 TTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATTTCCAATGATTGTGAACTCCAC
 GCTGGCACATGCATGACTTTTTTC
 CACTCCTTCCTGATCGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACCATGTGG
 GACTGTATGGAGGTCGCTGGCCA
 AACCATGTGCCTTACTGTCTTCATGATGGTCATGGTGATTGGAAATCTAGTGgtatgtagc
 aaaaacatttctcattt
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54

exon 17 (formerly exon 14)

gtttcatttagcaatgatttcagtattttctgcaatgactaataagcaaatagtgataatagtatttttatattgacc
 aagcatttttatttcattcacttttttcagaatagtgtatcatgaattagcagaaatgcattgtagaataaaataaggt
 gtcaagaacaatcttagaaaactaatgatggaagcaattgaagcaatagaatgtttgatcacctgttttctgctgt
 gtttcagGTTCTGAACCTCTTCTTGGCCTTGCTTTTGAGTTCCTTCAGTTCTGACAATCTTG
 CTGCCACTGATGATGATA
 ACGAAATGAATAATCTCCAGATTGCTGTGGGAAGGATGCAGAAAGGAATCGATTTT
 GTTAAAAGAAAAATACGTGAATTT
 ATTCAGAAAGCCTTTGTTAGGAAGCAGAAAGCTTTAGATGAAATTAAACCGCTTGAA
 GATCTAAATAATAAAAAAGACAG
 CTGTATTTCCAACCATAACCACCATAGAAATAGGCAAAGACCTCAATTATCTCAAAGA
 CGGAAATGGAACCTACTAGTGGCA

58

exon 21 (formerly exon 18)

aaattcttaggcctttcccaaaacttactaagtcagactctgctattggtgttttaacaagaccctgggtgattttga
 aactcatgaaagtcgagaattactgattcattgcatagagcaaggctgaactgtgtagacatttttatatgtaataag
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59

exon 22 (formerly exon 19)

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60

exon 23 (formerly exon 20)

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61

exon 24 (formerly exon 21)

taaaacatgcttagataaattaaaaactcactgatgtactttttgtgaacaagtagatataatggttacaattcttc
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⁶²
exon 25 (formerly exon 22)

tcgataagcttttaagcaattaataattcagatagcatgttttgataatttttagtctagaaatatgactaatatggcat
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⁶³
exon 26 (formerly exon 23)

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⁶⁴
exon 27 (formerly exon 24)

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[illegible]

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AGCACCTTGAAGGAAACAACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCT
GAAGACAGCGTCAAAAGAAGCAGC
TTCCTTTTCTCCATGGATGGAAACAGACTGACCAGTGACAAAAAATTCTGCTCCCCT
CATCAGTCTCTCTTGAGTATCCG
TGGCTCCCTGTTTTCCCAAGACGCAATAGCAAAACAAGCATTTTCAGTTTCAGAGG
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TTGAAGAATCTAGACAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCT
TGATCTGGGACTGCTGTGATGCA
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ATCTTTGATGGAATTATTGTCAGCCTCAGTTTAATGGAGCTTGGTCTGTCAAATGTGG
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TCATTTAGCTCAGACAACCTTGCTGCTACTGATGATGACAATGAAATGAATAATCTG
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AAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAAAAAGCCTTTTT
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TCCATGAAGGCAATAAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATA
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TTAAGAGCTTTAAGACCTCTAAGAGCCTTATCCCGGTTTGAAGGCATGAGGGTGGTT
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TCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTGATCTTTAGCATC
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TTACAATGCAATGAAGAACTTGGATCCAAGAAACCTCAGAAACCCATACCTCGCC
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ACTGTGACCCTGACACAATTCA
CCCTGGCAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGGATTTTCTTTTTT
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TCCTGGTGgTGGTGAACAGTTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTA
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AGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGGAAAAGTTTGATCCCGaTGCG
ACCCAGTTTATAGAGTTCTCTAA
ACTCTCTGATTTTGCAGCTGCCcTGGATCCTCCTCTTCTCATAGCAAAACCCAACAAA
GTCCAGCTTATTGCCATGGATC
TGCCCATGGTCAGTGGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAA
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GAGATGGATGCCCTTCGAATACAGATGGAAGACAGGTTTATGGCATCAAACCCCTC
CAAAGTCTCTTATGAGCCTATTAC
AACCACCTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATTGAGCGTAATTT
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atttttaaagacaatttggatctaaatatgtatttcataattctcccataataaattatataaggtggctaa

Seq. Id. No. 66 (cont'd)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDNENKPKPNSDLEAGK
 NLPFIYGDIPPEMVSEPLEDL
 DPYYINKKTFIVMNKGKAI SRFSATSALYILTPLNPVRKIXKILVHSLFSMLIMCTILTNC
 VFMTLSNPPDWTKNVEYT
 FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLD FSVIVMAYVTEFVDLGNVSALRTRV
 LRALKTISVIPGLKTIVGAL
 IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGTMD
 SNGTFVNVTMSTFNWKDYIG
 DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPNGYTSFDTFSWAFLSLFRL
 MTQDYWENLYQLTLRAAGKTY
 MIFFVLVIFLGSFYLVNLILAVVAMAYEGQNQATLEEAQKEAEFQQMLEQLKKQQEEA
 QAVAAASAASRD FSGIGGLGE
 LLESSEASKLSSKSAKEWRNRKRKRRQREHLEGNNKGERDSFPKSESEDSVKRSSFLFS
 MDGNRLTSDKKFCSPHQSL
 SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENFADDEHSTFEDSESRRDSLFPVPHRHGERR
 NSNGTTTETEVRKRRLSSY
 QISMEMLEDSSGRQRAVSIASILTNTMEELEESRQKPPCWYRFANVFLIWDCCDAWLK
 VKHLVNLIVMDPFVDLAITC
 IVLNTLFMAMEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPYYYFQEGWNIFD
 GIIVSLSLMELGLSNVEGLSV
 LRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAHVIFAVVGMQLFGKSYKE
 CVCKINDDCTLPRWHMND
 FHSFLIVFRVLCGEWIETMWDCMEVAGQTMCLIVFMLVMVIGNLVVLNLFALLSSFS
 SDNLAATDDDNEMNNLQIAVG
 RMQKGIDYVKNKMRECFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGN
 GTTSGVGTGSSVEKYVIDEND
 YMSFINNPSLTVTVPIAVGESDFENLNTTEFSSESELEESKEKLNATSSSEGSTVDVVLPRE
 GEQAETEPEEDLKPEACF
 TEGCIKKFPFCQVSTEEGKGKIWWNL RKT CYSIVEHNWFETFIVFMILLSSGALAFEDIYI
 EQRKTIKTMLEYADKVFTY
 IFILEMLLKWVAYGFQTYFTNAWCWLD FLIVDVSLVSLVANALGYSELGAIKSLRTLRA
 LRPLRALSRFEGMRVVVNALV
 GAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNM TGTGNMFDISDVNNLSDCQALG
 KQARWKNVKVNF DN VGAGYLA
 LLQVATFKGWMDIMYAAVDSRDVKLQPVYEENLYMYLYFVIFHFGSFFTLNLFIGVIID
 NFNQQKKKFGGQDIFMTEEQ
 KKYYNAMKKLGSKKPQKPIPRPANKFQGMVDFVTRQVFDISIMILICLNMVTMMVET
 DDQGYMTLVLSRINLVFIVLF
 TGEFVLKLVSLRHYYFTIGWNIFDFVVVILSIVGMFLAEMIEKYFVSPTLFRVIRLARIGRI
 LRLIKAGK GIRTLLFALM

MSLPALFNIGLLLFLVMFIYAIFGMSNFAYVKKEAGIDDMFNFETFGNSMICLFQITTSAG
WDGLLAPILNSAPPDCDPD
TIHPGSSVKGDCGNPSVGIFFFVSYIIISFLVVVNSYIAVILENFSVATEESAEPLEDDFEM
FYEVWEKFDPDATQFIE
FSKLSDFAAALDPPLLIAPNKVQLIAMDLPMVSGDRIHCLDILFAFTKRVLGESGEMDA
LRIQMEDRFMASNPSKVSYE
PITTTLKRKQEEVSAIIQRNFRCYLLKQRLKNISSNYNKEAIKGRIDLPIKQDMIIDKLNG
NSTPEKTDGSSSTTSPPS
YDSVTKPDKEKFEKDKPEKESKGKEVRENQK.

Seq. Id. No. 67 (cont'd)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDNENKPKPNSDLEAGK
NLPFIYGDIPPEMVSEPLEDL
DPYYINKKTFIVMNKGKAISRFSATSALYILTPLNPVRKIXKILVHSLFSMLIMCTILTNC
VFMTLSNPPDWTKNVEYT
FTGIYTFESLIKILARGFCLEDFTLRDPWNWLD FSVIVMAYVTEFVSLGNVSALRTRFVL
RALKTISVIPGLKTIVGAL
IQSVKKLSDV MILTVFCLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGTMD
SNGTFVNVTMSTFNWKDYIG
DDSHFYVLDGQKDLLCGNGSDAGQCPEGYICVKAGRNPNGYTSFDTFSWAFLSLFRL
MTQDYWENLYQLTLRAAGKTY
MIFFVLVIFLGSFYLVNLILAVVAMAYEGQNQATLEEAEQKEAEFQQMLEQLKKQQUEEA
QAVAAASAASRDFSGIGGLGE
LLESSSEASKLSSKSAKEWRNRKKRRQREHLEGNNKGERDSFPKSESEDSVKRSSFLFS
MDGNRLTSDKKFCSPHQSL
SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENFADDEHSTFEDSESRRDSLFPVPHRHGERR
NSNGTTTETEVKRRLSSY
QISMEMLEDSSGRQRAVSIASILTNTMEELEESRQKCPPCWYRFANVFLIWDCCDAWLK
VKHLVNLIVMDPFVDLAITC
IVLNTLFMAMEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPYYYFQEGWNIFD
GIIVSLSLMELGLSNVEGLSV
LRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAHVFIFAVVGMQLFGKSYKE
CVCKINDDCTLPRWHMND
FHSFLIVFRVLCGEWETMWDCMEVAGQTMCLIVFMLVMVIGNLVVLNLFLALLSSFS
SDNLAATDDDNEMNNLQIAVG
RMQKGIDYVKNKMRECFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGN
GTTSGVGTGSSVEKYVIDEND
YMSFINNPSLTVTVPIAVGESDFENLNTEEFSSSESELESKEKLNATSSSEGSTVDVVLPRE
GEQAETEPEEDLKPEACF
TEGCIKKFPCQVSTEEGKGKIWWNLRKTCYSIVEHNWFETFIVFMILLSSGALAFEDIYI
EQRKTIKTMLEYADKVFTY
IFILEMLLKWVAYGFQTYFTNAWCWLD FLIVDVSLVSLVANALGYSELGAIKSLRTLRA
LRPLRALS RFEGMRVVVNALV
GAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDVNNLSDCQALG
KQARWKNVKVNF DN VGAGYLA
LLQVATFKGWMDIMYAAVDSRDVKLQPVYEENLYMYLYFVIFHFGSFFTLNLFIGVIID
NFNQQKKKFGGQDIFMTEEQ
KKYYNAMKKLGSKKPQKPIPRANKFQGMVFDVTRQVFDISIMILICLNMVTMMVET
DDQGKYMTLVLSRINLVFIVLF
TGEFVLKLVSLRHYYFTIGWNIFDFVVVILSIVGMFLAEMIEKYFVSPTLFRVIRLARIGRI
LRLIKGAKGIRTL LFALM

MSLPALFNIGLLLFLVMFIYAIFGMSNFAYVKKEAGIDDMFNFETFGNSMICLFQITTSAG
WDGLLAPILNSAPPDCDPD
TIHPGSSVKGDCGNPSVGIFFFVSYIIISFLVVVNSYIAVILENFSVATEESAEPLEDDFEM
FYEVWEKFDPDATQFIE
FSKLSDFAAALDPPLLIAPNKVQLIAMDLPMVSGDRIHCLDILFAFTKRVLGESGEMDA
LRIQMEDRFMASNPSKVSYE
PITTTLKRKQEEVSAAIQNRNFRCYLLKQRLKNISSNYNKEAIKGRIDLPIKQDMIIDKLNG
NSTPEKTDGSSSTTSPPS
YDSVTKPDKEKFEKDKPEKESKGKEVRENQK.

Seq. Id. No. 68 (cont'd)

Seq. Id. No. 69

exon 01 (formerly exon 00a)

aatgtatttatttaattgatgataaactgtaataaatcatagttgttgcctctaaagtagatatgaaaggtcagatgaa
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 atatcctaataaataatattagctaggttcaactgatgtatagaatcttttctacatttagatatttcttgc aaatgtt
 taccagaaagcaacacaaaaatactatcagtgagtatgtgttacactgttcttaaggagc aaatctcctcaccttgaa
 aataattcatcccaggaagagaaaaagggttttcaaaagactagagcaggccacaaggagc tttcgcaaaactctacacgt
 aaagggtaatgtaaacttaaaacatTTTTTcaaacagtaatttatatacttttaatttttagtagtttatgtgtgaaac
 aatcatgcaaaacaacaaagtataaaatTTTTTaaaaaaatttagtgagatgcaataactgaatatgtaaaagggtcga
 tacatatttatatgtagtagataagttacatttttttagtgtgttgggaaatttttagctcacatcacctctctactgtca
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 ATAAGCA
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 AAATTGTA ACTAATTTGTAAACCT
 CTGTGGTCAAAAAAAAAAAAAAAAAAAAAAAAAAGCTGAACAGCTGCAGAGGAAGACAC
 GTTATACCCTAACCATCTTGGATGC
 TGGGCTTTGTTATGCTGTAATTCATAAGGCTCTGTTTTATCAGgtaagctgacaaaacatttcattatc
 tgcaccataga
 acctagctaccaggctatttcttactttaaaatcatcttcatgctgctattttaaccagtggtttaaagttaa
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 aatattttttattatactta

70

exon 01b (formerly exon 00b)

agggagaacagaaggatgctcaggagtgccagcatgccttcagaaagactaaatggatcaaggctgccaaagaaggggg
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 acaagggtcaaatatcttgcattgcatcatcctgtcttctcgatccagggccataaaaaaaaaagggaataaaaccaga
 cacagagccagagcaccctatgccaaatgtcaagattataggctaatttcacctgtattctctttctacagAGATTAT
 GGAGCAAGAAA ACTGAAGCCAAGCCACATCAAGGTTTGACAGGGATGAGATACCTG
 TCAAGGATTCATAGTAGAGTGGCT
 TACTGGGAAAGGAGCAAAGAATCTCTTCTAGGGATATTGTAAGAATAAATGAGATA
 ATTCACAGAAGGGACCTGGAGCTT
 TTCCGGAAAAAGGTGCTGTGACTATCTAAGgtaactaaacaacttctgggtataagttgtttttgtggaaaataaa
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72

73

Seq. Id. No. 71 - 73

74

exon 04 (formerly exon 03)

gagtgacaccaaggccatcacaggcttgaagttcttattttatcattgttttaaaacaataatattaattca
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 TCCTGACTGGACAAAGAATGTAGAgtaagtaggaataactctgggaatgagaatgcacactcaaattctctagcaatc
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75

exon 05 (formerly exon 04)

aaaatttaccatttgygctttccattacatttctatcagataactctgcgctagtaggtcaaactagatgattatccat
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 TTGCTTAGAAGATTTTACGTTTCTTCGTGATCCATGGAAGTGGCTGGATTTCAGTGTC
 ATTGTGATGGCgtgagtaactt
 tgaaaattgataagcgcaaaggagtgaaaatagtcatagtacaacaaggctttgtgtcatatattaaatgtagagct
 ttctgttagtcaagttaactatatgggtgtgtattttcagaatacatattagaatacatattgcaatgtaaatatatac
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76

exon 06N (formerly exon 05N)

attgtttaaactcacagggtctatgtgccaaccagcattaagtccttatttagtataaactttgccaaaactatcag
 taactctgatttaattctgcagGTATGTAAACAGAATTTGTAAGCCTAGGCAATGTTTCAGCCCTTCG
 AACTTTTCAGAGTC
 TTGAGAGCTCTGAAAACCTATTTCTGTAATCCCAGGtaagaagaactgggtgaaggtagtaggcccttata
 tctccaac
 ttttctgtgtgtattgtgtgtgtgtgaactccctattacag

77

exon 06A (formerly exon 05A)

gtaagaagaactgggtgaaggtagtagggcccttatatciccaacttttctgtgtgtattgtgtgtgtgaact
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 TCAGAGTTCTCCGAGCAC
 TGAAAACAATTTTCAGTCATTCCAGgtgagagctaggttaaacaccgaggtgactttaattattgagttgaaatcaatt
 tataatgacttacagcattagccttgtgtcttattattacagttcatcccggtaaataatgccaaatgatgttcaatgtc
 agtttagctcctaaaaattttataaattacatgcgtatttataaagtcagcctttgagtttaacagaaaattgcatgagac
 atcttcaaaaaatgctaatttgggcctcttgcgctctctctctcttttactaccatggctttactaacagatttgg
 attttaccattcgctgcagatgtagttcaaaaatg

78

exon 07 (formerly exon 06)

aaacttcctgactagatatttaaaccttcattgaattccagcaagcacactgttcatgtgtaaaatctgctgttcat
 ctatttcccaaatcatcaggctatccatacagctttgggtgctaaatagtcagcaatcatttatgggggaaagagaatg
 tgttgactattaagaaatcatgatttctggcactcttctcaggtaacctatagttctctctgcagGTTTAAAGACC
 ATTGTGGGGGGCCCTGATCCAGTCGGTAAAGAAGCTTTCTGATGTGATGATCCTGACT
 GTGTTCTGTCTGAGCGTGTTTGC
 TCTCATTGGGCTGCAGCTGTTTCATGGGCAATCTGAGGAATAAATGTTTGCAGTGGCC
 CCCAAGCGATTCTGCTTTTGAAA
 CCAACACCACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAATG
 TAACAATGAGCACATTTAACTGG
 AAGGATAACATTGGAGATGACAgtaagaagtattacattatgtaacctagtggtgctgaatgaatttcaactataaa
 tagt

79

exon 08 (formerly exon 07)

tgagactgtgggtgtacagccaccttgtaaataactgaaatagccaactctgatttactaataactaatgtgaata
 ggattaatatgaaataaaatgggtttttttgtattaacagGTCACCTTTTATGTTTTGGATGGGCAAAAAGACC
 CTTTA
 CTCTGTGGAAATGGTTCAGATGCAGGgtaagaacataatatatttttaagatatagaactctttgcgaaaaaaaaa
 gtaggtaggaaaacaactacatggttatatgtgtagccttaccatgtatgcaataaagagcagtgctgctcccctaggaa
 gtgcctgtctgccttaccggattgccactggctctaaactcacagcaattaaaaattatcccttgtgaagaccttcc
 ccaaaatttcacagttaagatgttcttaattgatgtccaatgtgtgaaggcccagagtctgtctttgtgtacatcta
 tcagagctgttaggaaa

80

exon 09 (formerly exon 08)

aaagagtaaaaatatggtaaggtcagagccaaaagtgtgtggtgctagctttctgccattctaaatgtctrwaaawatt
 tatttgcactaaattttctatcgggtcttctagtgaaatttcactgtataagtttcacgggtgggcaatcacctaaagtgt
 tctggaaattaaagcaagataattcgtcacagatagcagctttgggtttgaaaattcctataagtcaataaaattgaaa
 ttgctgtaatttctaaactgacctacctccatttctctcttatagCCAGTGTCCAGAAGGATACATCTGTGTGAAGG
 CTGGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGGGCTTTCC
 TGTCTCTATTTGACTCATGACT
 CAAGACTACTGGGAAAATCTTTACCAGTTGgtaagggtccaaatgagcatgcataacatttattttatagacatgtatga
 aatgaaaagcataggctgagt

81
exon 10 (formerly exon 09)

agctaattagtctactgactatctaactgtggaatcagatatttatttggggacattataactaaatactgatggaatt
atccccatttcccctagACATTACGTGCTGCTGGGAAAACATACATGATATTTTTTGTCCTGGT
CATTTTCTTGGGCTC
ATTTTATTTGGTGAATTTGATCCTGGCTGTGGTGGCCATGGCCTATGAGGGGCAGAA
TCAGGCCACCTTGGAAGAAGCAG
AACAAAAAGAGGCCGAATTTTCAGCAGATGCTCGAACAGCTTAAAAAGCAACAGGAA
GAAGCTCAGgtactgagtataaa
mgcaagatttatcattattatmttagtttctaagtagaaatagtggtatactatagagggtagattggaactgtttt
tcattttatatatmggcattgtcattagacac

82
exon 11 (formerly exon 10a)

tgcaaactgttttcaaagctctgtgttctaaatagtcctggcttgttttatgacagGCAGTTGCGGCAGCATCAGCTG
CTTCAAGAGATTTTCAGTGGAATAGGTGGGTTAGGAGAGCTGTTGGAAAGTTCTTCAG
AAGCATCAAAGTTGAGTTCCAAA
AGTGCTAAAGAATGGAGGAACCGAAGGAAGAAAAGAAGACAGAGAGAGCACCTTG
AAGGAAACAACAAAGGAGAGAGAGA
CAGCTTTCCCAAATCCGAATCTGAAGACAGCGTCAAAAGAAGCAGCTTCCTTTTCTC
CATGGATGGAAACAGACTGACCA
GTGACAAAAAATTCTGCTCCCCCTCATCAGgtatgatttctactaagtgcctctgggttcttgcattgctattgctttt
tagttttgtattttgtttgttacactttgtactatctgtacttcagttgagggacaggaactaacatttaatatag
ttgtttaa

83
exon 12 (formerly exon 10b)

gtgaagactaaatgaagtgggtgtatacttagtaaattgcaaatcagtattgtagtcagaaaaacactctttgtactta
aatttgctttaataaaaaatatcaaaatatatgtgcctctataaatttgattatccatgtttaagggaagagtatacta
actccaaagaaaacagatcctttaataattaatatttataaataattgcttctccctacccccatccattcctttc
cttttgccttctctgcagTCTCTCTTGAGTATCCGTGGCTCCCTGTTTTCCCAAGACGCAATAG
CAAAACAAGCATT
TCAGTTTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGATGATG
AACACAGCACATTTGAAGACAGC
GAAAGCAGGAGAGACTCACTGTTTGTGCCGCACAGACATGGAGAGCGACGCAACAG
TAACgtagtcaggccagtagtc
atccagatggtgccagggtccagcaaatggggaagatgcacagcactgtggattgcaatgggtgtggttccctggtg
gggtgaccttcagctctaacgtcacctactgggcaactccccagaggtgataatagatgacctagctgctactgacatt
attaccaatttg

84

exon 13 (formerly exon 10c)

gaattctcttaaagggtactacctgtgatacttttttaaaaaaaactgtttataacttagcaataattcaatattttat
 tcttgaaattcttacctggaaaattgcatgtagcatgatttgcaaagaaatgctatgtggtgtgtattacttattggga
 agagtgggttgagccatcagatatttggttcagGGCACCACCCTGAAACGGAAGTCAGAAAGAGAAGG
 TTAAGCTCTT
 ACCAGATTTCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCCAAAGAGCCGTGAGC
 ATAGCCAGCATTCTGACCAACACA
 ATGGAAGgtaagagcaggtcatggaacagccaactttctgtgattatgtgcttgtgaactattccttctttcatagaa
 ttactgaagctgttaccagatcgaactatatattagacctaagaatgtgatatatggtgtacattatcacattgnnta
 caaaactaatattggccttattcttttgacttgggtccttaccttacttcagagtgatattcaacacttgatattat
 atcaat

85

exon 14 (formerly exon 11)

tagtcattttaaaagcaaaatattaaattcaaaagtgttatttctgtattcaaaagagaaaaagtcgatctatatgac
 attttaattaacattttctgaaaatatttaattgggattgtcttctcaagtgttctaagtaataatgaacttctattttcaa
 atataagcatcaattttgttaaataatgtaaaatctactagcaataataaactattttgtgttattactactcttcc
 ttgttattgtccctccagAACTTGAAGAATCTAGACAGAAATGTCCGCCATGCTGGTATAGATTT
 GCCAATGTGTTCTTG
 ATCTGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTAATTGTT
 ATGGATCCATTTGTTGATCTTGC
 CATCACTATTTGCATTGTCTTAAATACCCTCTTTATGGCCATGGAGCACTACCCCATG
 ACTGAGCAATTCAGTAGTGTGT
 TGACTGTAGGAAACCTGgtaagtacattgaagtttacttatttactttgtagatgtgggagagatagaccaaagggaa
 agatgtattttgtgctgtgtgaacccaaaaattatacctcttctcctcatagaaagaatatctaaggaatattacaggg
 aatctcagagatacagcctaaaactcaactggtatgaatgctgattgttaggccaatgtctgtgctgattgatcatggt
 gtcttaccagttgtaaacgtctcaaaa

86

exon 15 (formerly exon 12)

ctaagacttgaattgattgtcactattctcactttaaatttagatattttattcctgtctaattgttcttcttat
 aaattcgtgtagcatcagtgtttcagtgctcttgatagtagtgctgatctctaatttttagGTCTTTACTGGGATTTT
 TACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTATTtCCAAGAA
 GGCTGGAATATCTTTGATGGAA
 TTATTGTCAGCCTCAGTTTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGT
 ACTGCGATCATTACAGACTGgta
 tctatttataatataccctgtcgtccttggcacaacatttttgaattgaatcaatgtatatttatataattatta
 attttaattttaaatttacatcaaatgtgacattctaagaaaacatgtaaacatccyctttaaagctaaaccattttct
 aagaatgatgaagcattcaaaatactctataatgattaggtatgtagggcacattagaaaacctacaagtactttctaa
 aactgtgttttaagtttatgaagctttttggccttacagtcgtgaaagatacgcaataaaaaatttagacccagttaa
 ttttagctttttattaaccctact

87

exon 16 (formerly exon 13)

tatatttttttgcacttaaatgatattatgaccagattacaattctaattgttaacactatttttctggatttg
 aaattgaatcagttcagtatattttgagttttacatctaccacgtgtggttctatgataccacataactaataaaataat
 gtctaaaattatattatgattactactaacagcatcttttcacttgattacagCTTAGAGTTTTCAAGTTGGCAAAATCC
 TGGCCCACTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA
 AACCTCACCTTGGTGTGGCCAT
 CATCGTCTTCATTTTTGCTGTGGTTCGGCATGCAGCTCTTTGGTAAGAGCTACAAAGA
 ATGTGTCTGCAAGATCAATGATG
 ACTGTACGCTCCACGGTGGCACATGAACGACTTCTTCCACTCCTTCCTGATTGTGTT
 CCGCGTGTGTGTGGAGAGTGG
 ATAGAGACCATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT
 TTCATGTTGGTCATGGTCATTGG
 AAACCTTGTGgtatgtatgtagtacaaatgctcataaattagaacaagagcagacagtagctaggaacgtggccagatgt
 agtaaacatatctctgtttatagtaagtgccctagactgaaatccccctattagcactcagagaataagcaagttattt
 aacttctctgggctctgtgttccattt

88

exon 17 (formerly exon 14)

ccttagagcaggatattaggtcctttaagagtgtgtgacttagacatggcatctgaaatatagtaagcattcaataaac
 atttgtgaaataatttagcaaagatctatgagtcccttttaggctgtatttaaagcatttcaatattaarat
 aggcattttctttttcttttagGTTCTGAACCTCTTCTGGCCTTATTGTTGAGTTCATTTAGCTCA
 GACAACCTTG
 CTGCTACTGATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG
 CAAAAGGGAATTGATTATGTGAAA
 AATAAGATGCGGGAGTGTTCCTCAAAAAGCCTTTTTTAGAAAGCCAAAAGTTATAGA
 AATCCATGAAGGCAATAAGATAGA
 CAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAAGAGCTTAATTATCTTAG
 AGATGGGAATGGAACCAACCACTG
 GTGTAGGTACTGGAAGCAGTGTGAAAAATACGTAATCGATGAAAATGATTATATGT
 CATTATAAACAACCCAGCCTC
 ACCGTCACAGTGCCAATTGCTGTTGGAGAGTCTGACTTTGAAAACCTTAAATACTGAA
 GAGTTCAGCAGTGAGTCAGAACT
 AGAAGAAAGCAAGGAGgtaaggaatgctttaattttgttccatttctatgataaccatgtactacagttattac
 tattttcattgtgcttatatgcattatcgaaaxaagcaatgattgtaagt

89

exon 18 (formerly exon 15)

taattatttagtacataatgatcagtaagtctaatagagttaaatgctatcactacattttttcacacaatgacacagt
 atttcccagttagttaaataaaagggggaaaatcacatcttgaaatgggattttgttccagAAATTAAATGCAACCAG
 CTCATCTGAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCTG
 AAAGTGAACCCGAAGAAGACCTTA
 AACCGGAAGCTTGTTTTACTGAAGgtaacaagctctgatgtgattaaatacaatctccccctgttctttacggagactg
 aatatgcctcatfttaaaaaaaaaaatttagcaaacgaggtgtggtggcttatgcctgtaaccccaaaattttgggaggct
 acggtaggaggattgctgacccaggagttgagaccacctgggaaatgtagtaaggcttgcctctac

⁹⁰
exon 19 (formerly exon 16)

gaattctaagtagctggctgagtataataagctgagaataattcattatacaggagggatgctgacgataactaggaat
gaaggagatggttacctatgaaatgattacctggaagtggagtggggaaggggcaagaaagttatttttctattta
agattaaaatatatttttaattaactatatttsatttttagGATGTATTAAAAAGTTTCCATTCTGTCAAGTAAGT
ACA
GAAGAAGGCCAAAGGGGAAGATCTGGTGGGAATCTTCGAAAAACCTGCTACAGTATTGT
TGAGCACAACTGGTTTGAGACTTT
CATTGTGTTTCATGATCCTTCTCAGTAGTGGTGCATTGgtaagtgaatgcatattggcaagaatcagattct
ggtgaaat
agtttattctccaaaattaccagatgcaaacactgagcttcagaatcaaaagaaaaggcatatctgtgtcttcagagct
tggcaccgaaggttaacgatgcaaaattcagttctgaacaaatcagcaccatgaaacagccagatggaatttctcatct
ggtgtttatctaacagatgttttctcactgagacaaccatttgcagagacattctgtaacca

⁹¹
exon 20 (formerly exon 17)

ctagtttagtcttttagatttgtctcatgttcaatgtttatgtaaaatatcaataatcaaaattattctttgtactacta
ttatactaagcaatttttcaaatatttagaagaagcaagccatttaagtaaaataaaatattttgattcatagGCCTT
TGAAGATATATACATTGAACAGCGAAAGACTATCAAACCATGCTAGAATATGCTG
ACAAAGTCTTTACCTATATATTCA
TTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATATTTCACTAATGC
CTGGTGCTGGCTAGATTTCTTG
ATCGTTGATgtaagtattttaagtgtttttataaaattgttttaaaagaggcaagtttgacatttcatatgtttctgt
tattaaaactttcactaataatgacataattatgcagttatttaaaaaactgtaacatatgcaacaatgaggaatc
tcatgggaaaagtagaggaggtcctaaacatgggcagtg

⁹²
exon 21 (formerly exon 18)

ctaactaataatttaagcacacatccatgaaggatctggcattgaactcaatcctgaattatcagtggtatatgcacaag
ttgaaaaggggtccatggtataaaatatctaactggagatattgacacgtgttgataaatatgggcaagtattctggtt
cattggttaaaaaaagcaatagtagatgagactggcaatataagatgacccactatgtggaagatgaaagttgcc
aaggtagtccaaatagtagtctgcattaaatagataccacaccctataccttcagtcacagttatttcttg
tgaactaattaatttttttcttttagGTTTCTTTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCA
GAACTCG
GTGCCATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTATCCC
GGTTTGAAGGCATGAGGgtaaga
agaatagacactaattattcatgtcaaaaattacatgtaggtaatgatttagatagaaaaggggtgccatactcttctg
atatttatttcaatagaaattacagaattagaagc

93

exon 22 (formerly exon 19)

ccagcatacaacattttctgactccactctactataaccagggttttaatgatttctttcatactgtagcatatttgc
 ttctctaaaaccttagctcttttagttgtgtcattgtttgtttccttcaaataatgtgctagaaaaattagaagaacaa
 ctgtccacctagatttttatttaactctttcaagcacatattaactaaacaaatcattgaaggaaatggttccat
 tcaaaagggttgaagctatgttccctcgtgtctctcttagGTGGTTGTGAATGCTCTTGGTGGAGCAATTCCC
 TCTA
 TCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTGATCTTTAGCATCATGGGTGT
 GAATTTGTTTGCTGGCAAGTTC
 TACCACTGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTAAACAAT
 TTGAGTGACTGTCAGGCTCTTGG
 CAAGCAAGCTCGGTGGAAAAACGTGAAAGTAACTTTGATAATGTTGGCGCTGGCT
 ATCTTGCACTGCTTCAAGTGgtaa
 gtggctactgtacgagttttgaaaaagtttcaagatgtttcaaggaagattattccctgatgttctcgtttgaatga
 ctacatttgacagcatgaaaaaagttaatgataacacctataataatcagctgaattgatcataaaaaagatgttaca
 attattttataatgtattttccttagtgtaagcttttagtatgttttaatgtgattttatattct

94

exon 23 (formerly exon 20)

aaaggaaacaagtccagactttaatacaaatgttttctatttcaattttatttcaatctcttgatatgaaattcac
 aatattgtacaaaaagttattgttataatactgtcagattttcatctggttaaatgtcattgttaggtgaaattttat
 gaacaattcaaatatattgttttacagGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGT
 TGATTCACGAG
 ATgtaagtatcactcaaatattatttataggttctagatttctatgggtgaatattgggtgtaatttaaacactgataca
 tccaaaattctatattagaacatttaattgcatataaaaaatgaacagctcgttcaatatagatgatgcttgattaa
 tgtgtgcctaataatacaaatatgtagctaatatgaacg

95

exon 24 (formerly exon 21)

gtaaggcacaatgggaaaagagaatcaagaacaatcataaaacttgcaaaccttacttagatcatactagtttta
 aaaaattgtttttagaacaatatctcagggttaaggcaaaagtagcactgtattaagtaacagcactcaataaattact
 gatttagtgaagtatttatagattttcataatttttaataattttcaatatcatttagGTAAACTTCAGCCTGTATA
 TGAAGAAAATCTGTACATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTC
 TTCACTCTGAATCTATTTCATTG
 GTGTCATCATAGATAACTTCAACCAGCAGAAAAAGAAgataagtattcttttagcttttacctttcttctattct
 ggggttc
 tgtctgttaatacagccaaataaccagaataacctgtggtcatgacagacttaaatcatgtttatattttcagttgcc
 catgtggttatttaagctgcagggattccagcctctagtcagtggtcctctcaaagtttatctattggatagctttctg
 acccaaaaatgtgtccactccttcggacccatccaacgggtctccagtgttttagcttggttacagagccttcag

96

exon 25 (formerly exon 22)

acccttgcctacttttaacatagataatcaaattaggatcctgtagcgatcagagttttatgtacgtaaggatttt
 gcataatattaagatatcagaattcacataaatgggaaaagcaggataaatgtatatgtaggaggataatatccactt
 aaaaattagaaaagattaaaggaaagacaaatattttgtgaaagtactattggaacacagaattgtaaccagtttat
 actatgtctttacTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAATATTACA
 ATGCAATGAAGAACTTG
 GATCCAAGAAACCTCAGAAACCCATACCTCGCCCAGCAgtaagaattactgtctcctttaatgttccaaa
 gccatgcgt
 ccatatggcacaattgagcaatgctctggagcagaacatattaggtgatcaccaatattgagccctaattataaagt
 catatttgcataatcacactctgactcattaggagttaccacattcaaaaaaggaggtaattgtctttat
 aatttgtgagtgaaaacttctagctcagggttcctaataataacttcaaagcaaggtcacttctctgctacaa

97

exon 26 (formerly exon 23)

tatataaaccaaatatgctttgttagctatataaattttttccattttttaacatgaagagaaaaaagcacaca
 aaattgtttgggtaatatgaggagggtgcacatccatcccgatgtggaagggtttatctacaattttactgcattat
 tctttatgaatatatatagtaaccttattctctctcactttctagAACAAATTCCAAGGAATGGTCTTTGATTTT
 GTAACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAACATGGTC
 ACCATGATGGTGGAAACGGATGA
 CCAGGGCAAATACATGACCCTAGTTTTGTCCCGGATCAACCTAGTGTTTCATTGTTCT
 GTTCACTGGAGAATTTGTGCTGA
 AGCTCGTCTCCCTCAGACACTACTACTTCACTATAGGCTGGAACATCTTTGACTTTGT
 GGTGGTGATTCTCTCCATTGTA
 Ggtaagaacagcttaattaccaagaggtatagttacagagaacagttgccccaggaccttctagctgattaacatggaa
 attaggtctgagaataaatgcatatagatgtaaagttcaacactagcataattgaataaaaactctgaacctgggtt
 tattacaaaagctaactagttagaaccatgtaggaataaccagatttgggaaagaggtgaagaagacaggaaataaaca
 ttatcagggtactctctaattcttaaaccaaggtcacagg

98

exon 27 (formerly exon 24)

aatctgtaatgctaatagcaggagtgatccaaatatftaataaaggctcatattcataacaagttgtgtgttcatag
 accttaaaaaagataaagccatcatgtaaagtgaagatatattctgttttagctgtgttctatgtttccatagGTATG
 TTTCTGGCTGAGATGATAGAAAAGTATTTTGTGTCCCTACCTTGTTCCGAGTGATCC
 GTCTTGCCAGGATTGGCCGAAT
 CCTACGTCTGATCAAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGAT
 GTCCCTTCCTGCGTTGTTTAAACA
 TCGGCCTCCTGCTCTTCCTGGTCATGTTTATCTATGCCATCTTTGGGATGTCCAACTTT
 GCCTATGTTAAAAAGGAAGCT
 GGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATGATCTGCTTGTTTC
 CAAATTACAACCTCTGCTGGATG

GGATGGATTGCTAGCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACAC
 AATTCACCCTGGCAGCTCAGTTA
 AGGGAGACTGTGGGAACCCATCTGTTGGGATTTTCTTTTTTGTGAGTTACATCATCAT
 ATCCTTCCTGGTGgTGGTGAAC
 AGTTACATCGCGGTCATCCTGGGAGAACTTCAGTGTTGCTACTGAAGAAAGTGCAGAG
 CCCCTGAGTGAGGATGACTTTGA
 GATGTTCTATGAGGTTTGGGAAAAGTTTGATCCCCaTGCGACCCAGTTTATAGAGTTC
 TCTAAACTCTCTGATTTTGCAG
 CTGCCcTGGATCCTCCTCTTCTCATAGCAAAACCCAACAAAGTCCAGCTTATTGCCAT
 GGATCTGCCCATGGTCAGTGGT
 GACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGTGTTTTGGGTGAGA
 GTGGAGAGATGGATGCCCTTCG
 AATACAGATGGAAGACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCC
 TATTACAACCACTTTGAAACGTA
 AACAAGAGGAGGTGTCTGCCGCTATCATTGAGCGTAATTTGAGATGTTATCTTTTAA
 AGCAAAGGTTAAAAAATATATCA
 AGTAACTATAACAAAGAGGCAATAAAGGGGAGGATTGACTTACCTATAAAACAAGA
 CATGATTATTGACAAACTgAATGg
 GAACTCCACTCCAGAAAAAACAGATGGGAGTTCCTCTACCACCTCTCCTCCTTCCTA
 TGATAGTGTAACAAAACCAGACA
 AGGAAAAGTTTGAGAAAGACAAACCAGAAAAAGAAAGCAAAGGAAAAGAGGTCAG
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 aagaattatcttfgatcaattgtttacagcctatgaaggtaaagtatatgtgtcaactggacttcaagaggaggtcca
 tgccaaactgactgttttaacaatactcatagtcagtgccatacaagacagtgaagtgaacctctgtcactgcaact
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 tacctagactatagggatagttgtgcaagtgaaattgtaactacacaaacacctttagtagctcctgcatccatt
 ctatttttaactccatctgcatatttttacaattttgttctagtgcaattccatgggtcccaattcatagtttat
 tcataatgctatgtcactattttgtaaatgaggtttacgtgaagaacagtatacaagaacctgtctctcaaatgat
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 ctccattttctagatggctttaattttgaaagtatttttagctgttatgtttgttctatctgaacagttatgtgctg
 laaagtctcctctaataatttaaaggattattttatgcaaagtattctgttcagcaagtgcatttttattctaagttt
 cagagctctatatttaatttaggtcaaatgctttccaaaaagtaataataatccattctagaaaaatatctaaag
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 taaacaactctattaaatcaaatatgtaccacagtgatgtgtcttttgcaagcttccaacagggtatcctgtatc
 attcattaaacatagtttaaaggctatcactaatgcatgttaattgcctatgctgctctattttactcaatccattct
 tcacaagtcttggttaaagaatgtcacatattggtgatagaatgaattcaacctgctctgctcattatgtcaagcagaat
 aatttgaagctatttacaacacctttacttttgcaatttcaacatgagtatcatatggtagctctctagatttc
 aaggaaacacactggatactgcctactgacaaaacctattctcatattttgctaaaaatatgtctaaaacttgcgcgaa
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acaatttattttactttatgcttttgcttttgatttttaacacaaattccaaacttttgatccataagattttcaatg
gataatttcctaaaaataaaagttagataatgggttttatggatttctttgtataatatattttctaccattccaatagg
agatacattggtcaaactcaaacttagatcattttctaccaactatggttgctcaatataaccttttattcatagat
gttttttttattcaactttttagtattttacgtatgcagactagcttattttttaattcctgctgactaaagctat
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Seq. Id. No. 98 (cont'd)

Docket No.
CG/13180.18

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS, THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY.

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

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<u>60/167,623</u>	<u>November 26, 1999</u>
(Application Serial No.)	(Filing Date)
<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)
<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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